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UNUSUAL MANIFESTATIONS OF DISEASE

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THE MEDICAL CLINICS OF NORTH AMERICA

UNUSUAL CLINICAL AND LABORATORY MANIFESTATIONS OF DISEASE

CHARLES B. MOORE, M.D., *Guest Editor*

Volume 51 — Number 4

JULY, 1967

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Contributors to This Issue (Ochsner Clinic)

OSCAR J. BIENVENU, JR., M.D., Staff member, Section on Cardiology

H. M. BATSON, JR., M.D., Staff member, Section I, Department of Internal Medicine

ROBERT BIRCHALL, M.D., Head, Section I, Department of Internal Medicine

JOSEPH K. BRADFORD, M.D., Head, Section on Chest Diseases

WILLIAM P. COLEMAN, M.D., Head, Section on Allergy

W. D. DAVIS, JR., M.D., Head, Section on Gastroenterology

JULIO E. FIGUEROA, M.D., Staff member, Section I, Department of Internal Medicine

HURST B. HATCH, JR., M.D., Director, Pulmonary Physiology Laboratory and Associate Head, Section on Chest Diseases

HAROLD M. HORACK, M.D., Head, Section on Cardiology

JERRY D. JORDAN, M.D., Head, Section on Pediatric Cardiology and Associate Director, Cardiovascular Laboratory

KARL E. KELLER, M.D., Staff member, Section III, Department of Internal Medicine

T. R. KILPATRICK, M.D., Fellow in Cardiology, Alton Ochsner Medical Foundation

RONALD J. KNUDSON, M.D., Formerly Fellow in Surgery, Alton Ochsner Medical Foundation

RICHARD K. LANGE, M.D., Staff member, Section III, Department of Internal Medicine

WILLIAM LOCKE, M.D., Staff member, Section II, Department of Internal Medicine

CHARLES B. MOORE, M.D., Director, Cardiovascular Laboratory and Associate Head, Section on Cardiology

PAUL J. MURISON, M.D., Co-Director, Biophysics Laboratory and Associate Head, Section II, Department of Internal Medicine

F. SCOTT O'NEIL, M.D., Staff member, Section on Gastroenterology

GEORGE A. PANKEY, M.D., Head, Section on Infectious Diseases

GEORGE H. PORTER, III, M.D., Staff member, Section on Hematology

BERNARD F. RICE, M.D., Head, Endocrine Research, Section II, Division of Research, Alton Ochsner Medical Foundation

FRANK A. RIDDICK, JR., M.D., Staff member, Section II, Department of Internal Medicine

DON M. SAMPLES, M.D., Associate Head, Section on Hematology

ALBERT SEGALOFF, M.D., Head, Endocrine Research, Section I, Division of Research, Alton Ochsner Medical Foundation

THOMAS E. WEISS, M.D., Head, Section III, Department of Internal Medicine

PHILIP C. YOUNG, M.D., Associate Head, Section on Gastroenterology

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Erratum

Dr. Benjamin Burrows wishes to correct Equation 1, page 427 of the March 1967 issue, to read as follows:

$$\text{Rate of Gas Transfer} = \frac{\text{Coefficient of diffusion} \times \text{area}}{\text{Thickness}} \times \text{Pressure gradient}$$

RECENT SYMPOSIA

September, 1966 – *Nationwide*
Recent Advances in Medicine

November, 1966 – *Nationwide*
Hematologic Disorders

January, 1967 – *from Chicago*
Vascular Diseases

March, 1967 – *Nationwide*
Modern Management of Respiratory Diseases

May, 1967 – *from Jefferson Medical College and Pennsylvania State University*
What's New in Infectious Diseases – Prevention and Immunization

FORTHCOMING SYMPOSIA

September, 1967 – *Nationwide*
Efficacy of New Drugs
Howard F. Conn, M.D., *Guest Editor*

November, 1967 – *Nationwide*
Psychiatry for the Nonpsychiatrist
Ralph Kaufman, M.D., *Guest Editor*

January, 1968 – *from Chicago*
Pain and Its Clinical Management
James E. Eckenhoff, M.D., *Guest Editor*

March, 1968 – *from St. Louis*
Endocrine Disorders
William H. Daughaday, M.D.,
Thomas F. Frawley, M.D., *Guest Editors*

WILLIAM RANKIN ARROWSMITH, M.D.

Born August 19, 1910, at Scio, Ohio. B.S., Muskingum College, Ohio; M.D., Ohio State University, Columbus. Assistant in Research Medicine, Assistant in Anatomy, Moores and Ross Research Fellow, Ohio State College of Medicine, 1935–1938. Intern, Strong Memorial and Rochester Municipal Hospitals, Rochester, New York, 1938–1939. Resident and Assistant Physician, Barnes Hospital, St. Louis, 1939–1942. Assistant in Medicine, Washington University School of Medicine, St. Louis, 1939–1946. American College of Physicians' Research Fellowship, 1941–1942. Medical Corps, U.S. Army, 1942–1946. Staff, Ochsner Clinic, New Orleans, since 1946 and Head of the Department of Internal Medicine since 1951. Professor of Clinical Medicine, Tulane University School of Medicine, New Orleans. Consultant, Oak Ridge Institute of Nuclear Studies, 1950–1962 and Member of the Board of Directors, 1962–1964. Diplomate, American Board of Internal Medicine. Fellow of International Society of Hematology. Fellow of the American College of Physicians. Member, numerous medical bodies. Staff, Ochsner Foundation Hospital. Medical Consultant, Touro Infirmary. Senior Visiting Physician, Charity Hospital of Louisiana.

SYMPOSIUM ON UNUSUAL CLINICAL AND LABORATORY MANIFESTATIONS OF DISEASE

Dedicatory Foreword

This symposium appears at a time when the medical profession is again in the process of serious soul searching. Many believe that the proper relationship between the three major purposes of medicine—patient care, teaching, and research—has not been maintained. Excessive emphasis on research in medical schools has left less time for teaching and patient care by faculty members. A physician who has succeeded in maintaining a successful balance between these three aspects of medicine is Dr. William Rankin Arrowsmith, Head of the Department of Internal Medicine of the Ochsner Clinic.

In recognition of his role as the "complete" physician, this symposium on unusual clinical and laboratory manifestations of disease is dedicated to Dr. Arrowsmith, who has placed the quality of medical care above all other aspects of medicine and who has skillfully guided his Department through the critical years of its development. By his loyalty to each member of the Department, he has created an efficiently functioning group from a large number of distinct individualists. By his respect for the individual and acceptance of his colleagues as his equal until proved otherwise, he has encouraged harmonious cooperative effort among his staff providing the best possible medical care for our patients. By avoiding petty conflicts, he has been able to function more efficiently when confronted with major problems. By his identification with the field of internal medicine, he has raised immeasurably the stature of the Department of Internal Medicine at the Ochsner Clinic. As the first hematologist in our section of the country, he has made large contributions to the improvement in quality of medical care both in our organization and in other institutions in New Orleans.

As an internist, his first concern has always been for the patient—his care, feelings, and comfort. He is considerate of the patient and the patient's family to a degree attained by only a few. His "sixth" sense has made his diagnostic ability almost miraculous at times.

Dr. Arrowsmith excels in the preceptor type of teaching, being especially skillful in making the pertinent and practical points easily

understood and remembered. Since his primary concern is to provide the best patient care possible, he prefers to teach by example.

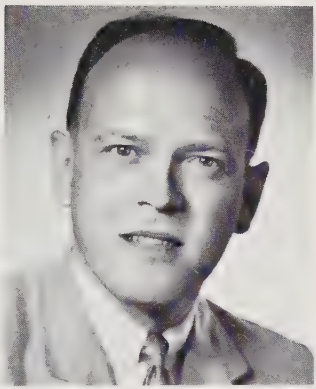
His inquiring mind and perceptive ability have been directed toward critical appraisal of the research work of others at the Clinic. His amazing quality of objective, critical examination of new advances in medicine has guided the members of his department through the years.

As evidence of the high esteem which his associates have for him, Dr. Arrowsmith was the first staff member, and the first internist, elected by the staff to the Board of Management of the Ochsner Clinic, which had previously consisted of the original five Founders, all of whom were surgeons. As a Board member, he has made an outstanding contribution to the growth and direction of the Ochsner Clinic. His keen, incisive mind, his thorough understanding of the Ochsner institutions, and his "great dissenter" approach to administrative affairs have been invaluable in the development of the cooperative effort in our group. He has, indeed, added balance to the administration of the Ochsner institutions. Despite his pressing administrative duties, he has always maintained a full schedule of clinical duties.

It therefore seems appropriate to dedicate this issue from the Ochsner Clinic to Dr. Arrowsmith, who for the past 20 years, has served as teacher, advisor, colleague, and friend not only to members of his own department but to our entire staff and the trainees of the Alton Ochsner Medical Foundation.

CHARLES B. MOORE, M.D.
Guest Editor

Preface



A striking fact evolved from preparation of this issue on unusual manifestations of disease. It early became apparent that what the general practitioner might consider an unusual feature of a disease would actually be a common manifestation to the physician specializing in that disease. Thus, few signs or symptoms of cutaneous disease are really unusual to the dermatologist. Therefore, it became my duty as guest editor, to decide what manifestations of the various diseases discussed I, as a practicing internist and cardiologist, would consider "unusual" and to suggest these for discussion by the contributors.

Certain subjects, although not actually unusual features of a disease, seemed appropriate for inclusion. For example, the article on hypertension was included because of the unusual symptoms that may develop from treatment with the various drugs used today.

Preparation of a volume such as this requires considerable effort of many people. Particularly notable among these is Miss Selma DeBakey, Director of the Department of Medical Communications of the Alton Ochsner Medical Foundation, to whom each author is personally indebted for her invaluable assistance and advice in the preparation of the individual manuscripts. In addition, I wish to acknowledge the untold hours of editing, correcting, and counseling which Miss DeBakey spent in assisting me in the final preparation of this issue. I would also like to express my sincere appreciation to the publishers, who are responsible for the final appearance of the volume.

Charles B. Moore, M.D.
Guest Editor

Ochsner Clinic
1514 Jefferson Highway
New Orleans, Louisiana 70121

Primary Aldosteronism

Unusual Manifestations and a Practical Approach to Diagnosis

ROBERT BIRCHALL, M.D.

H. M. BATSON, JR., M.D.

The past two decades have witnessed a renaissance of interest in arterial hypertension. Four things have brought this about: (1) the advent of many new drugs in the treatment of hypertension, (2) recognition of renal arteriolar stenosis as a cause of hypertension, (3) recognition of the importance of the juxtaglomerular apparatus, and clarification of the renin-angiotensin mechanism, and (4) description by Conn,[2] in 1955, of primary aldosteronism as a cause of hypertension.

There are two major situations in which hypertension is associated with abnormal production of aldosterone. The first, primary aldosteronism, occurs when there is an adrenocortical adenoma which secretes aldosterone excessively, pathologically, and inappropriately. The second, secondary aldosteronism, occurs when there is excessive production of renin by the juxtaglomerular apparatus. In the case of hypertension due to renal arteriolar stenosis, the stimulus is decreased "pressure" or "stretch" in the afferent arteriole as it reaches the glomerulus.[10] In malignant or premalignant hypertension, the stimulus is created by multiple intrarenal "blocks."[8]

The purpose of this paper is to describe primary aldosteronism with emphasis on the importance of its early recognition, to describe methods of diagnosis, in particular a relatively simple screening test, and to discuss presently available methods of differentiating primary from secondary aldosteronism. Four brief case histories will illustrate the great variability of the clinical picture and pathologic alterations.

INCIDENCE

The true incidence of primary aldosteronism is not yet known. Conn cited observations of Shamma and co-workers[9] relating to the presence

From the Department of Internal Medicine, Ochsner Clinic, New Orleans, Louisiana

of an adrenocortical adenoma greater than 1.5 cm. in diameter in 20 per cent of necropsies of hypertensive patients, as compared with only 1.8 per cent in necropsies of normotensive subjects. Based on this and other indirect evidence, such as demonstration of increased aldosterone excretion in a certain number of "essential" hypertensive patients, decreased renin secretion in certain hypertensive patients without renal arterial stenosis, development of hypokalemia after thiazides, and the relation of "maturity onset" diabetes to hypokalemia, Conn[4] believed the incidence of primary aldosteronism to be about 20 per cent.

Since we have not routinely measured aldosterone or renin, we cannot confirm or deny Conn's observations. The fact that hypokalemia frequently develops after administration of chlorothiazide scarcely proves the presence of a functioning adrenal adenoma. We recently reviewed more than 1,000 necropsy protocols, selecting 100 which met Shamma and co-workers'[9] criteria for hypertension. The incidence of adenomas of the size and description acceptable by these authors was only 3 per cent. In a review of the necropsy protocols of 100 consecutive normotensive persons, we found no adenomas which would fit their criteria. Our estimate of the true incidence of primary aldosteronism as the cause of hypertension would probably not be more than 3 per cent.

NATURAL HISTORY

Figure 1 depicts the natural history of aldosteronism projected in time. The adenoma probably grows slowly. When it finally becomes large enough to produce a pathologic amount of aldosterone, the initial event

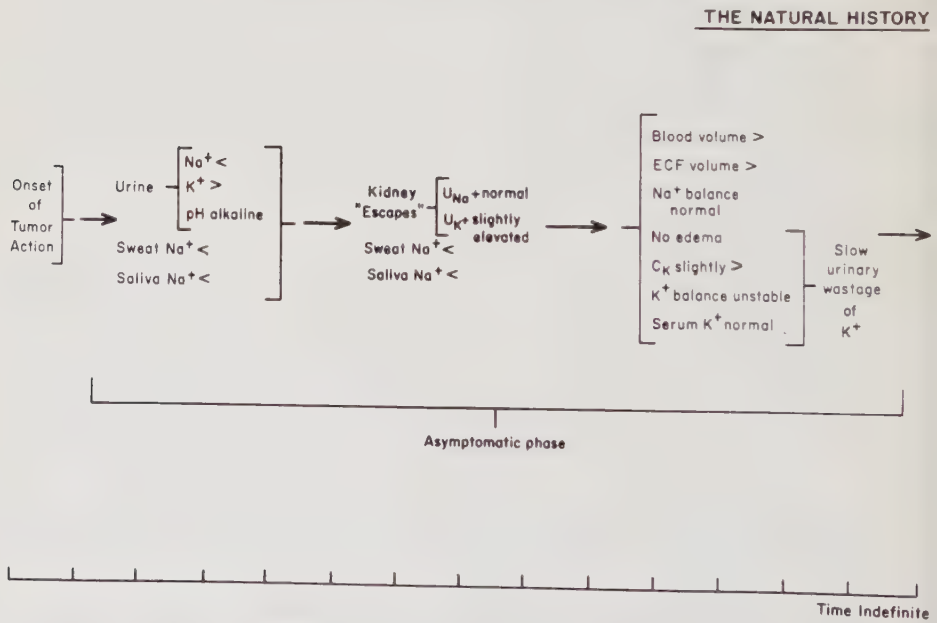


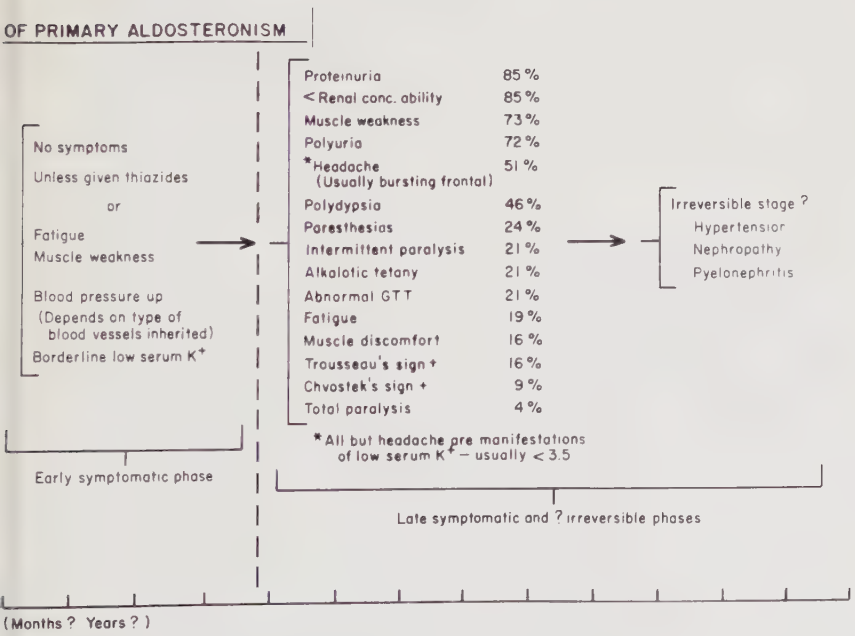
Figure 1. Schematic representation of the natural history of primary aldosteronism projected in time.

is a decrease in sodium concentration in the urine, sweat, intestine, and saliva, and an increase in urinary excretion of potassium. After three or four days, during which the blood and extracellular fluid volumes gradually, but permanently, increase, the kidneys "escape" and urinary sodium concentration returns to normal. Urinary potassium excretion, however, remains slightly above normal, and sodium concentration in sweat and saliva remains low. There then follows a slowly progressive urinary loss of potassium. The renal clearance of potassium will always be slightly high, and potassium balance in the body unstable, but for many months the serum potassium level may remain normal. Sometime during this period, depending probably on inherited vascular reactivity, the blood pressure will become elevated. Gradually, the full picture develops. All symptoms, except possibly headache, are due solely to hypokalemia.

DIAGNOSIS

If one agrees that aldosteronism develops gradually, it is obviously mandatory to make the diagnosis before the terminal stage, when damage is irreparable. For this reason, aldosteronism should be suspected in all patients with hypertension. Since few physicians are in a position to measure aldosterone or renin accurately, Conn's diagnostic triad of hypertension, overproduction of aldosterone, and underproduction of renin is impractical.[3, 4]

A more practical approach is to determine the response of secretion of aldosterone to dietary manipulation. A normal person responds to a



low sodium diet by releasing aldosterone, and to a high sodium diet by suppressing this release. This response is mediated through the renin-angiotensin-aldosterone mechanism, whereby a decrease in blood volume produces increased granularity of the juxtaglomerular cells, release of renin, formation of angiotensin I, and finally of angiotensin II, which is the single strongest stimulus for release of aldosterone.[8] Essentially, in normal persons, excretion of aldosterone is increased by a decrease in serum sodium concentration; an increase in serum potassium level; excessive potassium intake; adaptation to a hot, humid environment; and by nervousness and anxiety. Excretion rate normally varies from 3 to 32 mcg. in 24 hours.

In the patient with an actively secreting adenoma, production of aldosterone is pathologic in that it is totally independent of both diet and changes in blood volume. Thus, the "switch" is continuously set for the renal tubular exchange of potassium for sodium. The magnitude of the exchange depends on the number of sodium ions delivered to the renal tubule. Thus, a low-sodium diet yields low excretion of urinary potassium, and a high-sodium diet, high excretion of urinary potassium. Resistance to attempts at potassium repletion is great; yet the response of serum potassium to either a low-sodium diet or to administration of spironolactone is prompt.

Therefore, the potassium clearance or urinary excretion of potassium in a normal person on a high-sodium diet would be totally unaffected by addition of spironolactone, since secretion of aldosterone would be completely suppressed. Conversely, administration of spironolactone to a patient with a functioning adenoma, whose potassium clearance or urinary potassium excretion was high because of the high-sodium diet, would result in a prompt fall in potassium excretion or clearance.

This is the physiologic basis of the test we use routinely to exclude aldosteronism as the cause of hypertension. Our method for performing the test is as follows:

I. First Phase—Four days
   A. Regular diet with 9 gm. sodium chloride (weighed in special vial) to be added at table each day.
   B. On fourth day collect 24-hour urine specimen and measure K^- excretion.
   C. On morning of fourth day, draw blood for serum K^+.*
II. Second Phase—Three days
   A. Continue regular diet with addition of 9 gm. sodium chloride.
   B. Prescribe spironolactone, 75 mg. four times a day, and continue through the remaining three days of the test.
   C. On third day collect 24-hour urine specimen for K^+ excretion.
   D. On morning of third day draw blood for serum K^+.*
III. Calculation

$$\frac{U_K \times 24 \text{ hr. vol.}}{P_{K+}} = 24 \text{ hr. } C_{K+}{}^*$$

B. $$\frac{\text{Pre-spironolactone } C_{K+}}{\text{Post-spironolactone } C_{K+}} = \text{Aldosteronism Ratio}$$

*Serum K^+ not drawn in midpoint of 24-hour clearance for technical reasons.

Table 1. *Compilation of Renal K^+ Clearance Data on Four Patients with Evidence of Aldosteronism and of a Normal Control Subject*

	PRE-SPIRONOLACTONE					POST-SPIRONOLACTONE					
	PLASMA K^+ (MEQ./L.)	URINE K^+ (MEQ./L.)	URINE VOL. (CC./MIN.)	URINE VOL.* (CC./MIN.)	C_{K^+} (CC./MIN.)	PLASMA K^+ (MEQ./L.)	URINE K^+ (MEQ./L.)	URINE VOL. (CC./MIN.)	URINE VOL.* (CC./MIN.)	C_{K^+} (CC./MIN.)	RATIO PRE / POST
Control	4.5	62.5	0.67	0.54	7.5	4.5	70.0	0.90	0.73	11.4	0.66
Case 1	2.4	35.0	1.56	1.75	22.8	3.6	17.5	1.37	1.53	7.2	3.2
Case 2	3.6	57.0	1.53	1.25	19.8	3.2	5.8	2.57	2.11	3.8	5.2
Case 3	3.2	33.5	2.06	1.59	16.7	4.4	16.6	1.66	1.28	4.8	3.5
Case 4	3.1	21.1	1.81	1.54	10.5	3.4	9.0	2.03	1.73	4.5	2.3

*Corrected to 1.73 sq. m. surface area.

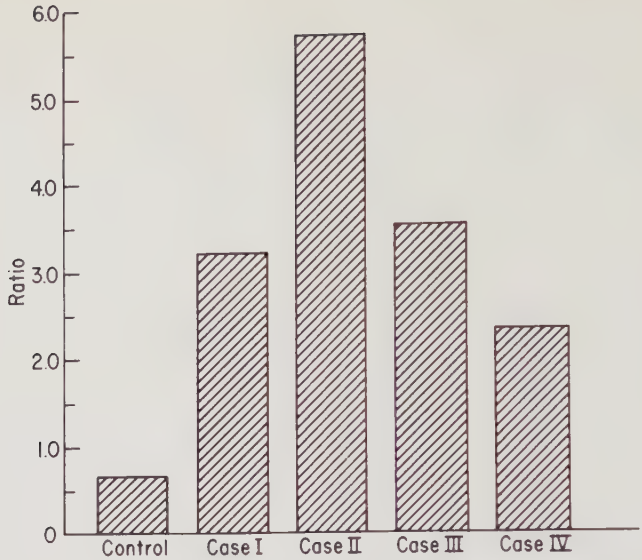


Figure 2. Comparison of the ratio of the 24-hour renal clearance of potassium on a high-salt diet before and after administration of spironolactone in 4 patients considered to have aldosteronism with that of a normal control subject.

Fortunately, the test can be performed either on hospitalized patients or on outpatients, and other tests can be done concurrently.

The result is calculated as the comparative renal clearance of potassium before and after addition of spironolactone (Table 1). Expressing the result as the renal clearance of potassium is more accurate than expressing it as 24-hour urinary potassium excretion, since the clearance automatically corrects for a low-serum potassium level. For convenience, we express the result as the ratio of the potassium clearance obtained before addition of spironolactone divided by the potassium clearance obtained after addition of spironolactone. At present, we believe that a ratio greater than 2 is diagnostic (Fig. 2).

DIFFERENTIAL DIAGNOSIS

Once it is determined that a patient either has persistent hypokalemia or is secreting a pathologic amount of aldosterone, it is necessary to eliminate all other possible causes. These include treatment with thiazide diuretics, geophagia, excess ingestion of licorice, renal acidosis, Cushing's disease, malignant hypertension, hypertension secondary to renal arteriolar stenosis, congenital hypertrophy of juxtaglomerular cells, and even thyrotoxicosis. Most of these are easily recognizable and a differential diagnosis can be made in summary fashion.

Hypertension due to renal arteriolar stenosis that has in turn produced secondary aldosteronism can present a difficult differential diagnostic problem.[5] In primary aldosteronism the hypertension is usually mild; serum sodium concentration is elevated; serum potassium level

is low and symptomatic. In secondary aldosteronism, the converse is true. Hypertension is severe, but serum sodium concentration is normal or slightly low, and the hypokalemia, which is rarely severe, is usually asymptomatic. Plasma renin and circulating angiotensin are increased. For this reason, the angiotensin infusion test[6, 7] is of theoretic interest. This test depends on the blood pressure response to a graduated infusion of angiotensin, the theory being that the geometric addition of X amount of angiotensin to a patient with a high circulating level of angiotensin (secondary aldosteronism) will have little effect on the blood pressure. Addition of X amount of angiotensin to a patient with no circulating angiotensin (primary aldosteronism) will have a pronounced effect on the blood pressure. Since, in our experience overlap occurs, the reliability of the test has not yet been established. Therefore, primary reliance must be placed on the dehydrated-hydrated intravenous pyelogram, renogram, differential clearance, and aortogram.[1]

The clinician would feel more comfortable if the problem of hypertension and aldosteronism always followed the classical pattern that has just been presented. To illustrate the difficulties that one can expect to encounter, four cases will be briefly presented. Case 1 is an example of a typical patient following the prescribed course. The other three cases, in which evidence of hypertension and pathologic secretion of aldosterone was clear-cut, illustrate the confusing variations in clinical course and pathologic alterations that may be encountered.

REPORT OF CASES

CASE 1. A 38-year-old white woman was first seen at the Ochsner Clinic in July 1964 with a two-year history of muscular cramps and stiffness, and a more recent history of extensive muscular weakness, hypertension, and cardiac irregularity. The blood pressure ranged from 130/80 to 228/122 mm. Hg. On admission, the patient was experiencing such severe muscular weakness that she was unable to raise her head off the pillow.

The serum potassium concentration was 113 mEq./L.; sodium 145 mEq./L.; chloride, 101 mEq./L.; and CO_2 capacity 37 mm./L. The urine was dilute with a pH of 7.0. Excretory urography, ^{131}I renography, renal arteriography, thyroid function studies, urinary 17-ketosteroid determination, and vanylmandelic acid determinations yielded normal results. The urinary aldosterone excretion was 62 mcg. in 24 hours (normal, 3 to 32). Dietary manipulation studies were consistent with a diagnosis of aldosteronism. The potassium clearance on a high-sodium diet was 22.8 cc./min. and fell to 7.2 cc./min. after administration of spironolactone was begun (Table 1 and 2 and Fig. 2).

At operation 19 months ago, a well-defined adenoma of the left adrenal was discovered. The gland was removed. The adenoma measured 3 by 2.5 by 2.5 cm. The postoperative convalescence was complicated by bleeding, followed by thrombophlebitis. The patient's blood pressure remained normal in the hospital. The serum potassium concentration initially rose to 6.1 mEq./L. and then fell to low normal readings, but one month later it was again normal and has remained so. The patient has felt well during the 18 months after operation and her blood pressure and serum potassium have remained normal.

CASE 2. A 50-year-old white man was seen at the Ochsner Clinic in July 1963 because of chronic gout and diastolic hypertension for ten years. The patient was treated with reserpine and chlorothiazide for hypertension during the two years before admission. A hypertensive evaluation, including hydrated and dehydrated

intravenous pyelography, ^{131}I renography, differential clearance studies, renal arteriography, vanylmandelic acid determination, and thyroid function studies, failed to demonstrate a lesion capable of producing elevations of the blood pressure. The serum potassium level, however, which was 2.9 mEq./L. initially, remained low despite administration of potassium supplements, and the serum sodium level initially was 150 mEq./L. The patient was treated for more than one year with various antihypertensive agents and potassium supplements, but the serum potassium concentration remained persistently low.

In November 1964 he was admitted to the Ochsner Foundation Hospital for dietary manipulation and further observation. The blood pressure during hospitalization averaged 190/110. Serum potassium concentration was still consistently low. The 24-hour potassium clearance before administration of spironolactone was 19.8 cc./min. compared with 3.8 cc./min. after the patient had been taking spironolactone. The ratio was 5.2 (Table 1 and Fig. 2). The 24-hour urinary aldosterone excretion was 21 mcg. (normal range, 3 to 32).

At abdominal exploration a large left adrenal gland with nodular hyperplasia was noted. The right adrenal gland was smaller but also hyperplastic and nodular. The left adrenal gland and two-thirds of the right gland were removed. Postoperatively, hypertension has persisted, though the course is much more benign, the average pressure being 160/110. Serum potassium concentration has been consistently normal, usually above 4.5 mEq./L., and the patient has felt remarkably relaxed and well. No obvious cause for the diffuse nodular hyperplasia of both adrenal cortices could be demonstrated.

CASE 3. A 30-year-old white man was admitted to Ochsner Foundation Hospital in December 1965 because of severe diastolic hypertension for six months. Studies elsewhere were reported to demonstrate low serum potassium concentration and increased aldosterone excretion.

On admission to Ochsner Foundation Hospital the blood pressure was 196/126 and remained in this high range throughout his hospitalization. General hypertensive evaluation revealed no evidence of renal arterial disease. Results of tests for pheochromocytoma were normal, as were 17-ketosteroid and plasma cortisol determinations. Serum potassium concentration was consistently low, ranging between 3.2 and 3.7 mEq./L., though the serum sodium level and serum carbon dioxide content were normal. The urine concentrated satisfactorily and was usually acid. The potassium clearance after a high-salt diet was 16.7 cc./min. and after spironolactone it was only 4.8 cc./min.; the ratio was 3.5 (Table 1 and Fig. 2). Urinary aldosterone excretion was 28 mcg. in 24 hours.

At abdominal exploration an enlarged left adrenal gland was noted, but no nodule was found. The right adrenal gland was normal. The left adrenal gland was removed, as was a portion of the right. Pathologically, both glands were normal.

Postoperatively, the patient remained hypertensive. Serum potassium concentration remained in the low or low-normal range. We have no explanation for either the severe hypertension or the persistently low serum potassium concentration.

CASE 4. A 58-year-old white man had been a patient of the Ochsner Clinic for ten years. Annual physical examination showed him to be in good general health, and his blood pressure and serum potassium concentration were always normal. In July 1963, the patient had acute pancreatitis, followed by multiple pseudocysts of the pancreas. During this illness, his serum potassium concentration was repeatedly in the range of 2.4 mEq./L. In January 1964 mild elevation of blood pressure was noted on routine examination; hypertension evaluation, including dehydrated and hydrated excretory urography and ^{131}I renography, all of which yielded normal results, was undertaken. The electrocardiogram showed only a slight abnormality, low T waves being present. The serum potassium concentration ranged between 3.3 and 4.0 mEq./L. on repeated examinations despite numerous attempts to keep it within the normal range by administration of potassium supplements. The serum sodium ranged between 143 and 146 mEq./L. The 24-hour urinary aldosterone excretion was 16 mcg., normal range being 3 to 32.

In June, 1965, the patient was admitted to Ochsner Foundation Hospital, where further investigation, including renal arteriography, demonstrated no renal arterial stenosis. An angiotensin infusion test yielded information suggestive of a diagnosis of primary aldosteronism. Serum concentration potassium was persistently low (3.2 to 3.5 mEq./L.).Urine was constantly dilute and alkaline; the serum carbon dioxide content, however, was normal. A salt-loading test followed by administration of spironolactone yielded information suggestive of a diagnosis of aldosteronism (Table 1 and Fig. 2). Cholelithiasis, discovered incidentally, had been suspected but not demonstrated at the time of the attack of pancreatitis.

At abdominal exploration in late June 1965, no adrenal adenoma was found; however, the left adrenal was removed, as it was definitely larger than the right. There was nothing to suggest an aldosterone-secreting tumor pathologically. The gallbladder was removed.

The patient has had normal blood pressure and normal serum potassium concentration on repeated examinations since operation. Yet neither grossly nor microscopically do the pathologic alterations in the resected adrenal gland offer any explanation for the low serum potassium level, nor do they explain the persistently normal serum potassium level and blood pressure in the 13 months since operation.

SUMMARY

Primary aldosteronism is a potentially curable cause of arterial hypertension. Its incidence, though uncertain, is estimated to be about 3 per cent.

The natural history of aldosteronism is one of insidious onset and slow progression with hypernatremia; slight but permanently increased blood and extracellular fluid volume; hypokalemia; and excretion of dilute, alkaline urine. Hypertension is typically mild and may develop at any time. Specific symptoms of hypokalemia develop late.

A practical approach to the diagnosis of aldosteronism involves determination of 24-hour renal K^+ clearance in patients on a high sodium diet before and after administration of spironolactone. The C_{K^+} pre/post spironolactone ratio should be above 2 to be diagnostic.

Differentiation between primary and secondary aldosteronism basically requires exclusion of renal arterial stenosis, renal parenchymal disease, and other unusual causes of secondary aldosteronism. Hypernatremia is the rule in the primary form, hyponatremia in secondary aldosteronism. The angiotensin test may prove to be helpful in differentiating the two forms, but its status remains to be clarified.

Four cases of patients, three presenting unusual manifestations or diagnostic pitfalls, are presented. Each patient was considered to have pathologic secretion of aldosterone.

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Primary Hyperparathyroidism

FRANK A. RIDDICK, JR., M.D.*

The clinical and pathologic manifestations of primary hyperparathyroidism vary widely. For this reason, it is perhaps incorrect to speak of unusual manifestations. Many patients do not present the stereotyped picture of osteitis fibrosa cystica, multiple renal calculi, or both. In these patients the diagnosis may be overlooked.

PATHOLOGIC VARIATIONS

Hyperparathyroidism is produced by increase in the quantity of circulating parathyroid hormone. In secondary hyperparathyroidism, the parathyroid glands are overactive in response to some stimulus, either hypocalcemia or hyperphosphatemia, and the resulting secretion of parathyroid hormone serves to maintain the concentration of ionized calcium in body fluids at a point where tetany is absent or minimal even at the expense of pathologic alterations in bone.

In primary hyperparathyroidism, autonomous hyperfunction of one or more glands leads to an excess of parathyroid hormone, causing changes in bone and other tissues, and to hypercalcemia, with its effect on kidneys, eyes, and other tissues. There may be an adenoma of one or more glands, hyperplasia of the chief cell variety or of clear cell type usually involving more than one gland, or carcinoma. The oxyphil cell of the parathyroid gland has long been considered to be nonsecretory, but we recently encountered enlarged parathyroid glands in which the only abnormality was pronounced nodular proliferation of oxyphil cells in a patient with hyperparathyroidism.

Because surgical removal of all hyperfunctioning parathyroid tissue is optimal treatment for primary hyperparathyroidism, the possibility of pluriglandular disease must be realized. Except in patients with endocrine adenomatosis and some instances of familial hyperparathyroidism, it is impossible to predict preoperatively whether a patient has a single adenoma, multiple adenomas, or hyperplasia. Meticulous dissection in the neck with identification of all parathyroid tissue is mandatory if cure is to be achieved in hyperparathyroidism. In our

*From the Department of Internal Medicine, Ochsner Clinic, New Orleans, Louisiana

series 21 of 78 patients had either primary hyperplasia of more than one gland or multiple adenomas, and would not have been cured by removal of a single diseased parathyroid gland.[13, 17] Cope[4] found pluriglandular disease in 16 per cent of his patients.

At times, multiple adenomas are not contemporaneous. An occasional patient will, after adequate exploration and removal of a single parathyroid adenoma, have remission of hyperparathyroidism only to become hypercalcemic, months to years later, as the result of another parathyroid adenoma. In some of these patients, the pathologic diagnosis is primary chief cell hyperplasia rather than adenoma. Cutler and co-workers[5] called attention to the occurrence of pseudoencapsulation in hyperplastic parathyroid glands. Streaming of hyperplastic cells into the surrounding fat resembles a thin rim of compressed normal parathyroid tissue and leads to an erroneous diagnosis of true adenoma, especially when only one gland is involved. The distinction seems important, as recurrence is more likely with hyperplasia than with adenoma.

A mixed picture of primary and secondary hyperparathyroidism can exist in two groups of patients.[8] In one, primary hyperparathyroidism causes renal damage severe enough to produce chronic renal failure. Eventually, the persistent hypersecretion of parathyroid hormone from an adenoma is insufficient to maintain normal levels of ionized calcium in the face of excessive phosphate retention, and healthy parathyroid tissue is stimulated and becomes hyperplastic. Removal of parathyroid tissue will probably not benefit a patient so afflicted unless osseous disease is incapacitating. In the second group, adenoma and autonomous hyperfunction occur in a previously hyperplastic parathyroid gland in a patient with chronic renal failure or one with steatorrhea. In the few patients in whom this situation has been documented, a patient with chronic primary renal disease accompanied by uremia, acidosis, hyperphosphatemia, and hypocalcemia is discovered to have become hypercalcemic and is found to have an adenoma as well as generalized hyperplasia of the parathyroid glands. Autonomous hyperfunction of parathyroid glands has been reported in a high percentage of patients after successful renal homotransplantation for chronic renal insufficiency.[14] Although the process was self-limited in some patients, parathyroidectomy was required in others.

ANATOMIC FACTORS

Variability in both number and location of parathyroid glands is well known. This is of importance only when one of the unusually located glands has become diseased. Fortunately, most primarily diseased parathyroid glands are encountered in the retrothyroid area of the neck.

Every reported series contains some patients with hyperparathyroidism who required several operations to locate the disease. In our experience, parathyroid adenomas which were difficult to locate have been found as high as the angle of the mandible, attached to sheath of

the carotid artery, in the thorax attached to parietal pericardium just above the diaphragm, between the cervical spine and the esophagus, and buried within the substance of either thymus or thyroid gland.

Preoperative Localization

Normal parathyroid glands are small (combined weight 120 mg.) and are buried deep in the neck, behind the thyroid gland. Even when pathologically enlarged, they are rarely palpable. This led Fuller Albright to formulate the dictum, since known as Albright's law, "If a lump is palpated in the neck of a patient with hyperparathyroidism, the lump is a thyroid nodule." Despite this rule, preoperative localization by physical examination or radiography is possible at times.

In six of 89 cases which we reported, enlarged parathyroid glands were detected preoperatively. In two, enlarged parathyroid glands caused indentation of the barium-filled esophagus (Fig. 1). In a third, an upper mediastinal shadow interpreted as a substernal goiter proved at operation to be a large parathyroid adenoma.

Three patients had masses in the neck which were found to be parathyroid adenomas. In one asymptomatic patient, the mass was far anterior and superficial, and seemed so characteristic of a thyroid nodule that desiccated thyroid was administered for six months in an attempt to shrink it. Only after she experienced renal colic did we undertake the studies which led to the correct diagnosis.

Figure 1. Cervical esophagram. The large indentation on the left (between the arrows) was caused by the lower parathyroid gland. The very large indentation on the right (between the arrows) was caused by a huge, cystic, right lower parathyroid gland. (Reproduced from Riddick and Reiss.[17])

MULTIPLE ENDOCRINE ADENOMAS

In 1953, Underdahl and associates[19] called attention to a syndrome characterized by adenomas or adenomatous hyperplasia of pituitary, parathyroid, and pancreatic islets. They reported eight personal cases and collected 14 from published reports.

The "typical" patient with the syndrome has a relatively asymptomatic chromophobe adenoma of the pituitary, chief cell hyperplasia of the parathyroid glands accompanied by hypercalcemia, and an insulin-secreting pancreatic β-cell adenoma. Now recognized as part of the syndrome are: eosinophilic adenoma of the pituitary with acromegaly, non β-cell adenoma of pancreatic islets with peptic ulcertaion or diarrhea (Zollinger-Ellison syndrome), hyperthyroidism, nodular hyperplasia of the adrenal cortex, and aldosterone-producing adrenocortical adenoma.

Although the syndrome occurs sporadically as a rule, Ballard and associates[1] found multiple endocrine adenomas in 10 members of the same family. In 85 collected cases of multiple endocrine adenomatosis the parathyroid glands were involved in 68.

The incidence of the syndrome may be higher than suspected; we found four instances among 90 cases of hyperparathyroidism. One had a chromophobe adenoma of the pituitary and a parathyroid adenoma; another, multiple insulin-secreting islet cell tumors and primary chief cell hyperplasia of all four parathyroid glands; a third, acromegaly and primary chief cell hyperplasia of three parathyroid glands; and the fourth, repeated bouts of peptic ulceration, noninsulin-producing islet cell carcinoma, and primary hyperplasia of two parathyroid glands. This incidence is comparable to that at the Mayo Clinic, where at least nine of 343 patients with primary hyperparathyroidism seen before 1960 had multiple endocrine adenomas.[12]

Whether occurrence of thyroid carcinoma in a patient with hyperparathyroidism should be classified as an example of multiple endocrine tumors is conjectural, but a high incidence of thyroid carcinoma has been reported in patients with hyperparathyroidism. We have encountered this combination in only two patients, but eight of Gordan's 94 patients operated on for hyperparathyroidism were found also to have thyroid carcinoma.[9] Granted that exploration of the neck for parathyroid adenoma affords the surgeon opportunity for removal of thyroid lesions which might otherwise remain asymptomatic, the incidence in Gordan's series is much greater than that encountered in necropsy series.

FAMILIAL INCIDENCE

Occasionally, hyperparathyroidism is familial, and careful questioning about symptoms of renal lithiasis, peptic ulcer, and other evidence of hyperparathyroidism in relatives of patients with this disease may be fruitful in discovering additional cases. An example of such a family is shown in Figure 2. Discovery that two patients were

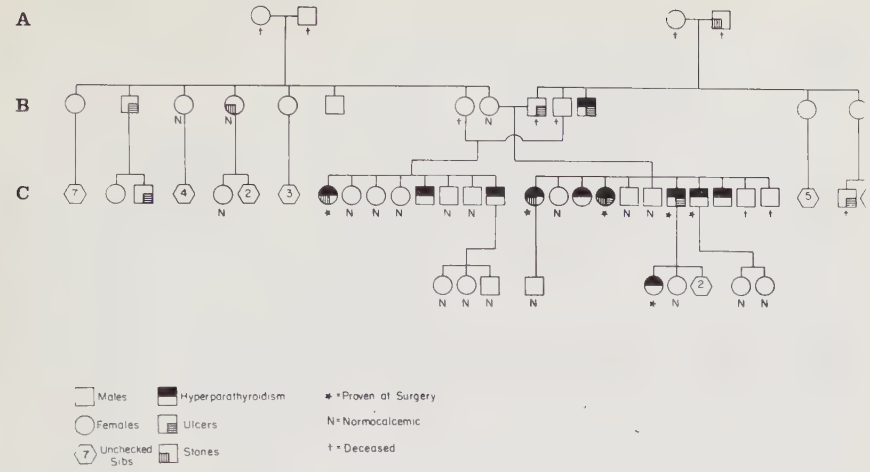

Figure 2. Pedigree of familial hyperparathyroidism. (Reproduced from Cutler, Reiss and Ackerman.[5])

sisters and a third was their cousin led to investigation of other members of the family, eight of whom proved to have hyperparathyroidism.[17] A high percentage of patients with familial hyperparathyroidism have primary chief cell hyperplasia rather than an adenoma of the parathyroid gland.[5]

PRESYMPTOMATIC HYPERPARATHYROIDISM

In recent years, clinicians have increasingly appreciated that hyperparathyroidism may often be detected in the asymptomatic person. This is not surprising, as overproduction of parathyroid hormone and the consequent hypercalcemia may exist for a variable period before producing detectable effect on renal or skeletal systems. In many patients in whom investigation of hypercalcemia led to a diagnosis of hyperparathyroidism, the reasons for initially obtaining the serum calcium determination are obscure.

Randall[16] reported the serendipitous discovery of hyperparathyroidism in 20 patients, many of whom were asymptomatic. Nearly 25 per cent of the 30 patients with hyperparathyroidism encountered in a five-year period were asymptomatic.[17] Perhaps the best example of discovery of this disease through detection of elevated serum calcium values is the study of Boonstra and Jackson,[2] who performed serum calcium determinations on every patient admitted during a five-year period. Of the 26,000 patients studied, 31 had primary hyperparathyroidism. Only eight had symptoms or signs which would have led to appropriate diagnostic studies under ordinary circumstances.

Asymptomatic or presymptomatic is not always a proper term for patients in this group, as often the patient does not appreciate the significance of vague symptoms attributable to hypercalcemia. Some

patients note in retrospect feeling tired and lackadaisical before diagnosis and cure of hyperparathyroidism.

CLINICAL MANIFESTATIONS

Psychiatric and Neurologic Symptoms

Alterations in mood, behavior, and mentation occur in hypercalcemic patients. In some patients with hyperparathyroidism, neuropsychiatric symptoms predominate.

The weakness and malaise experienced by patients with hyperparathyroidism may be incorrectly attributed to emotional factors until the diagnosis is established. At times, the hyperparathyroid patient experiences severe psychiatric symptoms. Apathy and depression are the most common; anxiety, paranoid ideation, severe agitation, and hallucinations are rare.

I recently examined a 42-year-old man whose only complaint was severe anxiety of brief duration. He had no stigma of hyperparathyroidism; the only abnormality discovered on extensive diagnostic studies was hypercalcemia. During several months of observation, no other pathologic process became evident, and removal of a parathyroid adenoma, 2 cm. in diameter, has apparently cured his extreme nervousness.

Neurologic symptoms caused by elevation of calcium level include motor weakness and hypotonia, fatigability, headache, lethargy, somnolence, and when hypercalcemia is severe, areflexia and coma.

Ocular Manifestations

Deposition of calcium in the cornea can at times be detected by slit-lamp examination in patients with hyperparathyroidism, as well as with other hypercalcemic states. The process, band keratopathy, characteristically occurs in the region of the palpebral fissure of the cornea. Hazy, grayish, granular epithelial and subepithelial deposits concentric with the limbus are most noticeable in the temporal and nasal areas, fading away toward the center. Usually a clear margin exists between the edge of the deposit and the limbus. When extensive, opacification of the cornea can be detected with the naked eye.

Calcium deposits in the bulbar conjunctiva are best detected by examination with the slit lamp. They resemble small, glasslike particles, usually found in the palpebral fissure area, close to the limbus.

Chalky white material may accumulate in the palpebral conjunctiva, and cause burning, tearing, and ocular irritation. Newman and Lawrence[15] suggested that respiratory exchange of oxygen and carbon dioxide across the mucous membranes of the eye leaves the conjunctiva relatively alkaline, which predisposes the tissue toward deposition of calcium salts.

Oral and Dental Manifestations

Although loss of the lamina dura of the teeth is considered pathognomonic of hyperparathyroidism, we have not found it helpful. In our

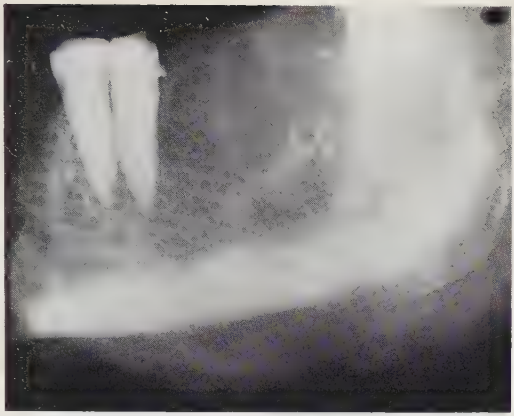

Figure 3. Radiograph of surgical specimen of benign giant cell tumor (epulis) removed from mandible of a 38-year-old woman with primary hyperparathyroidism. The lesion is multiloculated. New bone growth at the margins of the lesion distorts the mandible.

experience, the lamina dura is usually still present when diagnostic changes, such as subperiosteal bone reabsorption, are readily apparent on radiographic examination of the hands; furthermore, in almost every patient referred because of absence of the lamina dura on dental radiography this abnormality was the result of periodontal disease rather than hyperparathyroidism. Nevertheless, when osseous disease is far advanced, the teeth become loose and are lost either spontaneously or with minimal trauma.

Epulis, a giant cell tumor of the mandible or maxilla, may be the presenting complaint of the patient with primary hyperparathyroidism. Histologically, these tumors are similar to giant cell tumors of bone occurring elsewhere in the skeleton, both spontaneously and in patients with the osseous disease of hyperparathyroidism. Since they tend to occur intra-orally, the patient is more readily aware of their presence than he is of lesions in other bones. The patient often consults an oral surgeon or otorhinolaryngologist, who may consider the tumor an isolated lesion rather than a manifestation of a generalized skeletal disorder.

The diagnosis of hyperparathyroidism in one young woman we studied was established when the surgical pathologist, after examining the patient's third epulis of the maxilla in two years, suggested that the serum calcium and phosphorus values be determined. In another instance, a large, recurrent epulis (Fig. 3) was removed from the mandible of a 38-year-old woman. Tracheostomy is customarily performed on patients who have extensive mandibular resection, and the surgeon in so doing found that what appeared to be a 1.5 cm. nodule arising from the isthmus of the thyroid kept dangling into the operative field. The nodule, which proved to be a parathyroid adenoma, was excised, and postoperative study left no doubt that the patient had been suffering from hyperparathyroidism.

Skeletal Bone and Joint Symptoms

Osteitis fibrosa cystica, the classical osseous disease of hyperparathyroidism, is infrequently encountered in its full-blown state with

multiple fractures, skeletal deformities, and numerous large cysts and tumors of bone. A much more common skeletal observation is diffuse demineralization, often with scattered cystic lesions.

On occasion, the only evident abnormality is an isolated bone cyst or tumor. A 67-year-old retired naval officer recently seen had only a large, single, cystic lesion of the lower left femur. In another hospital, biopsy of the lesion was interpreted as a giant cell tumor of bone. The presence of hemosiderin caused the pathologist to raise the question of hyperparathyroidism. Unfortunately, the hypercalcemia was interpreted as suggesting the tumor might be malignant, and the bone tumor was widely excised, followed by application of a body spica cast. During the ensuing period of immobilization, rising serum calcium levels were accompanied by nausea, mental changes, and uremia. At the time of transfer to our institution, the patient was believed to be in a state of hypercalcemic crisis. Immediate parathyroidectomy was effective in lowering the blood calcium to normal levels.

Early osteitis fibrosa cystica may cause no symptoms. Discomfort and debility due to fracture of diseased bone are characteristic of the far advanced state. Isolated bone cysts may cause aching and mild discomfort. Rarely, bones are tender to palpation and light pressure.

In addition to pain in the bone, the patient with hyperparathyroidism may have articular discomfort. Stiffness and pain, effusion into the joints, and limitation of motion occur infrequently. Hyperparathyroidism causes at least four different forms of articular involvement.[3] The most common is related to resorption of bone near articular surfaces, leading to collapse of bone and deformity of articular cartilage. The radiologic observations resemble those of rheumatoid arthritis with resorption of bone about the articular surfaces. A second form is encountered in patients with metastatic calcifications; it is seen in other hypercalcemic states as well as in conditions in which hyperphosphatemia leads to deposition of calcium phosphate in tissues. Calcium salts are deposited in tendons and joint capsule. Calcification of synovial membranes may be extensive. Deposition of calcium in articular cartilage is unusual. This process, articular chondrocalcinosis, also occurs in persons without hyperparathyroidism and may cause the pseudogout syndrome, in which crystals of calcium phosphate in synovial fluid produce attacks of severe articular pain, inflammation, and effusion. A fourth form of articular pain and arthritis is gout, related to the hyperuricemia which occurs with increased frequency in patients with hyperparathyroidism.[18]

An extremely rare complication of hyperparathyroidism is avulsion of tendons from their insertions into bone. It is not clear whether the predisposing factor is alteration of bone by the disease, changes in connective tissue of the tendons induced by parathyroid hormone, damage to the tendon from calcium deposition, or some combination of these factors.

Renal Symptoms

Patients with hypercalcemia often have impaired ability to elaborate

concentrated urine. They have polyuria and hypostenuria unresponsive to injections of pitressin. These abnormalities lead to dryness of the mouth and thirst, which at times may be so severe as to suggest a diagnosis of diabetes insipidus. The underlying cause of the abnormality is most likely to be deposition of calcium in the medullary portion of the kidney. In experimental animals subjected to renal damage by hypercalcemia, the initial sites of calcification are the collecting ducts, the ascending limb of the loop of Henle, and the distal tubule.[7]

Repeated bouts of nephrolithiasis are well known manifestations of hyperparathyroidism. Many patients classified as having renal disease of hyperparathyroidism may have only a small asymptomatic stone or give a history of having passed a stone, often in the remote past. In two of our patients the only renal abnormality was a single episode of renal colic 18 and 25 years, respectively, before the diagnosis of hyperparathyroidism was established. Nephrocalcinosis is detected radiographically in patients with hyperparathyroidism with relative infrequency, but is often present microscopically in renal tissue removed at the time of nephrectomy or necropsy.

Renal failure with uremia and pronounced decrease in glomerular filtration rate occurs in some patients with hyperparathyroidism in the absence of renal lithiasis or detectable nephrocalcinosis. Multiple factors may be involved, but it is likely that deposition of calcium in renal tissue is the most important, as similar symptoms occur in patients with vitamin D intoxication, the milk-alkali syndrome, and hypercalcemia of malignant disease. In some patients severe hypercalcemia and dehydration and in others pyelonephritis contribute to deterioration of renal function. A direct nephrotoxic effect of parathyroid hormone itself has not been ruled out, and Dent,[6] who pointed out that renal failure is generally detected in patients with osteitis fibrosa cystica, postulated the existence of an osteitis fibrosa hormone, distinct from parathyroid hormone and capable of causing great damage to the kidneys.

Hypertension, which frequently accompanies hyperparathyroidism, is generally correlated with degree of renal impairment. In some patients blood pressure falls to normal levels after surgical relief of hyperparathyroidism.

Gastrointestinal Symptoms

As the concentration of ionized calcium in body fluids rises, patients may experience nausea, anorexia, vomiting, constipation, and vague abdominal pains. These are the presenting and predominant symptoms in some patients with hyperparathyroidism. Extreme elevation of serum calcium can cause gastric dilatation and paralytic ileus.

In addition, the incidence of peptic ulceration in patients with hyperparathyroidism is high. From 10 to 30 per cent of patients in various series have been so afflicted. In our experience[17] peptic ulceration, when present, has been a major cause of morbidity. Recurrent ulceration, bleeding, and perforation were major contributing factors in the death of two patients and necessitated frequent hospitalization

of four additional patients, two of whom required subtotal gastrectomy.

In a number of centers[4, 12] an increased incidence of pancreatitis has been discovered in patients with hyperparathyroidism, and the importance of pancreatitis as a diagnostic clue to underlying hyperparathyroidism has been emphasized. We have encountered pancreatitis in only two patients.

Symptoms of Hypercalcemia

The symptoms produced by hypercalcemia are not specific for hyperparathyroidism. Nevertheless, they can call attention to the hypercalcemic state and direct the physician toward appropriate diagnostic studies. In addition to those symptoms noted as psychiatric, renal, ocular, and gastrointestinal, hypercalcemia affects neuromuscular excitability. The Q-T interval of the electrocardiogram is shortened, and the patient with hypercalcemia is highly sensitive to the effects of digitalis. In one 78-year-old woman with hyperparathyroidism, the frequent occurrence of digitalis-induced cardiac arrhythmia made operation mandatory despite her age, cardiac disease, and relative freedom from skeletal and renal complications of her disease. Treatment of the heart disease was facilitated greatly by restoration of the normocalcemic state.

When concentration of ionized calcium in extracellular fluid rises to extreme levels, hypercalcemic crisis occurs. Anorexia and abdominal pain are followed by nausea and vomiting. The resultant dehydration is augmented by the initial polyuria, and oliguria and progressive azotemia develop. Confusion, delirium, and stupor are succeeded by obtundity and coma. Cardiac arrhythmias are frequently the cause of death. In our experience, carcinoma of the breast is the most common cause of hypercalcemic crisis, but hyperparathyroidism may produce this state, particularly if a patient with skeletal disease is immobilized

Tetany as a Symptom of Hyperparathyroidism

The most unusual diagnostic clue to the presence of hyperparathyroidism is tetany, occurring in the infant born to a mother with unsuspected hyperparathyroidism.[10] Presumably, hypercalcemia in utero suppresses the fetal parathyroid glands so that serum calcium level falls drastically when the infant is given a phosphate-rich diet of cow's milk.

Tetany is an indication of a parathyroid adenoma when spontaneous infarction of a parathyroid adenoma causes rapid relief of the hyperparathyroid state followed by a period in which the remaining atrophic parathyroid glands are incapable of maintaining serum calcium at normal levels.[11]

SUMMARY

Primary hyperparathyroidism is the state resulting from excessive and inappropriate release of parathyroid hormone from a neoplasm,

usually benign, or from adenomatous hyperplasia of one or more parathyroid glands. Variability in location of parathyroid tissue and the frequency (20 per cent) of pluriglandular involvement serve as a challenge to effective surgical therapy. Symptoms of hyperparathyroidism are related both to the direct effect of parathyroid hormone excess and to the hypercalcemia it produces. Symptoms may be absent or so mild as to be overlooked. There is a wide spectrum of systemic involvement which may bring the patient first to an internist, dentist, urologist, orthopedist, ophthalmologist, psychiatrist, gastroenterologist, or pediatrician. Awareness of the protean nature of the disease will facilitate early diagnosis and cure, and help prevent serious renal and skeletal consequences of the disease.

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Hyperfunctioning Adrenocortical Diseases

PAUL J. MURISON, M.D.

Rather than detailing the unsual manifestations of a disease, this discussion is concerned with uncommon causes of common symptoms. Adrenocortical pathologic states are rare but can be discovered if physicians are aware that the manifestations of hyperfunctioning adrenal diseases are among the most common seen. This presentation will consider approaches to common symptoms in an effort to detect diseases that frequently are fatal if the patient is not treated but can usually be controlled and the patient often cured if the condition is recognized. Analysis of these symptoms will also provide a systematic approach to differential diagnosis, which may uncover conditions beside the adrenal disease that are amenable to treatment or cure.

Figure 1 is a simplified diagram of normal adrenal steroid production and control. The three steroids, cortisol, the principal glucocorticoid, aldosterone, the primary mineralocorticoid, and 17-ketosteroids, weakly androgenic and anabolic when produced in excess, cause the pathophysiologic manifestations of hyperfunctioning adrenocortical diseases. Although overlapping of the clinical states produced may be considerable in individual patients, excess of only *one* corticosteroid is more usual, so that the suspected adrenal disease can usually be narrowed down to one of these three, which would thus indicate, on clinical grounds, the most appropriate studies. Corresponding to the three classes of corticosteroids, the diseases they create are:

1. *Cushing's syndrome*, which is caused basically by excess of cortisol. Catabolic processes predominate, protein wasting being the cause of the clinical picture of muscular weakness; thin bones, thin, easily damaged skin; the peculiar, centripetal obesity; mental symptoms; diabetic tendency; and because cortisol also has mineralocorticoid properties, hypertension.

2. *Primary hyperaldosteronism*, which is caused entirely by excess of aldosterone so that the pathologic state consists principally of hypertension and low serum potassium concentration.

3. *Adrenogenital syndrome*, which is caused by the androgenicity

From the Department of Internal Medicine, Ochsner Clinic, New Orleans, Louisiana.

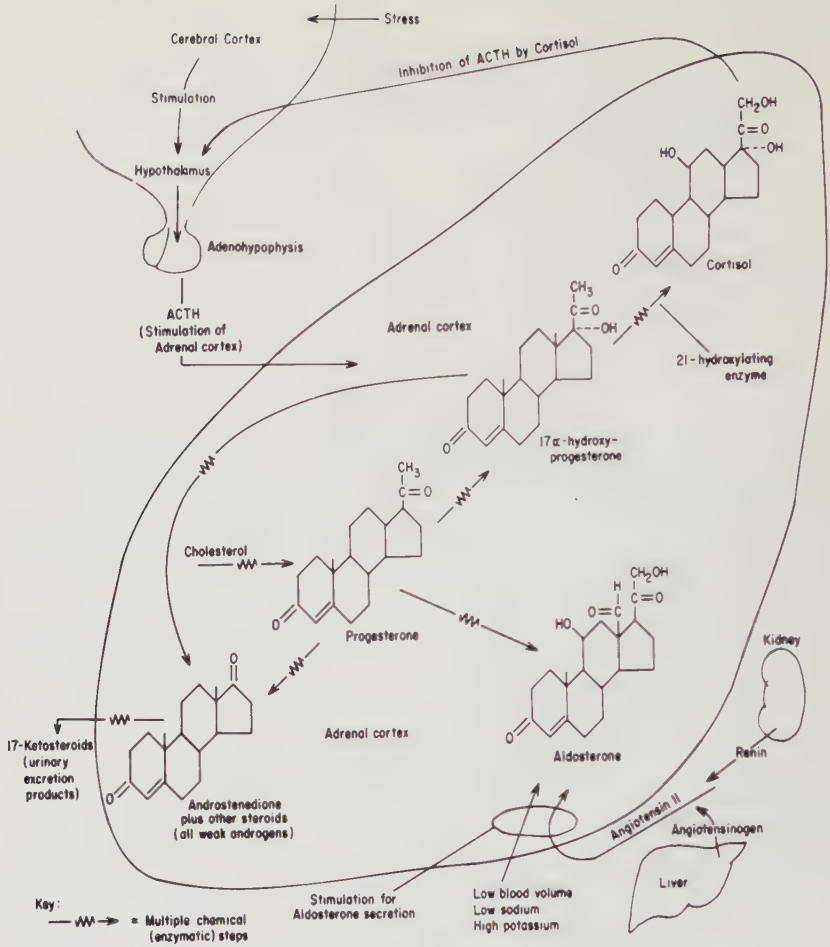

Figure 1. Simplified diagram of corticosteroid production and control.

of excess 17-ketosteroids. It is manifested by hirsutism and virilization in adults, and if present prenatally, mild to severe distortion of genital development in female newborn and older infants.

Simple listing of the symptoms produced by the hyperfunctioning adrenal cortex underlines the necessity of at least *considering the possibility of adrenocortical disease* in a large percentage of patients: obesity, hirsutism, weakness, hypertension, cutaneous disorders such as striae and acne, mental symptoms (irritability to psychosis), gonadal dysfunction (oligomenorrhea, amenorrhea, sterility, or impotence), osteoporosis, frank diabetes or diabetic glucose tolerance, and hypokalemia. The impression obtained from this imposing list of symptoms is one of overwhelming difficulty in determining which patients require further study. Discussion of each symptom, however, will show that this conclusion is unwarranted, since many clues can greatly narrow the field. Before these symptoms are considered, the differentials of the

Table 1. *Comparison of Clinical Picture and Steroid Assay of Hyperfunctioning Adrenocortical Diseases*

Disease	Hyperaldosteronism Aldosterone Excess	Cushing's Syndrome Cortisol Excess	Adrenogenital Syndrome Androgen Excess
Common Clinical Picture	Hypertension Weakness (Episodical) Other symptoms rare	Obesity Hypertension Weakness Hirsutism Thin bones Thin and florid skin Multiple symptoms	Hirsutism Virilism No "Cushingoid" features
Steroid Assay	17 OH N 17 KS N	17 OH ↑ to ↑ 17 KS N to ↑	17 OH N to ↓ 17 KS ↑ to ↑

N = Normal ↓ = Decrease ↑ = Moderate Excess ↑ = Great Excess
17 OH = 17-hydroxycorticosteroids 17 KS = 17-ketosteroids

three major classes of adrenocortical hyperfunctioning states will be outlined.

Table 1 shows the clinical pictures and steroid assays of the hyperfunctioning adrenocortical syndromes. All assays show change in the direction diagrammed, whether the assay method used is determination of secretion rate, blood level, or the most frequently performed 24-hour urinary excretion rate. The patient with hyperaldosteronism has normal 17-hydroxycorticosterone and 17-ketosteroid values. The patient with Cushing's syndrome has elevated 17-hydroxycorticosterone, but the level of 17-ketosteroids ranges from no elevation in those with mild hirsutism and no virilism to high in those with gross virilism; therefore, the picture may be confused with that of the adrenogenital syndrome. Differentiation is simple, however, since the 17-hydroxycorticosterone level in the androgenital syndrome is always normal. The final diagnosis, and from it, appropriate treatment, depend on demonstration of excessive production of one or more steroids, but usually this must be done indirectly by a number of tests, including hormonal assays. These will be considered in the discussion of each disease.

SYMPTOMS SUGGESTIVE OF HYPERFUNCTIONING ADRENAL CORTEX

Obesity is so common that even though 97 per cent of patients with Cushing's syndrome are obese, overweight might seem to be a worthless clue to this disease except that the type associated with Cushing's syndrome has several peculiarities. First, the fat is distributed centripetally, and unusual features are "buffalo hump" (prominent fat pads on the back of the neck) and "moon face" (prominent fat pads on the cheeks); the limbs are typically thin or spindly, a characteristic accentuated by the muscle wasting caused by the catabolic effect of excessive cortisol. Secondly, these patients are not extremely obese, rarely weighing more than 225 pounds.

Gonadal disturbance often becomes an important problem in exces-

sive secretion of cortisol plus variable amounts of androgen so that about 85 per cent of patients with Cushing's syndrome are affected. Since four of five patients with Cushing's syndrome are female, the presenting complaints are amenorrhea or at least oligomenorrhea while male patients usually are impotent. Gonadal disorder always is the major difficulty in the adrenogenital syndrome. In male infants macrogenitosomia praecox will initiate careful study, but in late childhood it may be missed or falsely attributed to hereditary virility. Even worse is failure to consider the rare masculinizing adrenal or gonadal tumors. Further danger arises from the physician's failure to consider the possibility of an accompanying salt-losing syndrome that one-third of these patients have. Especially in times of stress this defect can, if uncorrected, lead to a disastrous death.

Hirsutism is a major complaint of more than 70 per cent of patients with Cushing's syndrome and nearly 100 per cent of female patients with adrenogenital syndrome. In evaluation of this manifestation, the physician must consider change in pattern of hair growth, since the normal pattern in female persons varies widely and heavy growth is common and not necessarily abnormal. Therefore, the physician should avoid hinting to the patient that endocrine trouble is being considered as the cause, since in 95 per cent or more of women the pattern is inherited or the result of an individual idiosyncrasy of the hair follicles.

Hypertension occurs in 85 per cent of patients with Cushing's syndrome and 100 per cent of patients with primary aldosteronism. With our present knowledge careful study of *all* patients with blood pressure higher than 150/95 is imperative to detect the 10 per cent or more with curable hypertension (from renal vascular disease, adrenocortical hyperplasia, primary aldosteronism, or pheochromocytoma).[9] If mild to moderate hypertension is thought to be transitory, observation for several weeks or months with the patient taking only a mild sedative is a reasonable approach. Potent antihypertensive drugs will invalidate results of the various tests, and for this reason their administration should be withheld until the tests have been completed. Only mild sedatives should be given for two weeks before definitive studies are undertaken.

Mental symptoms, ranging from vague nervousness and irritability to psychoses, occur in about 60 per cent of patients with Cushing's syndrome and probably are due to concern about their appearance and weakness as well as direct action of cortisol on mental function. Great lability of mood is common; these patients typically are described as "difficult." The patient with adrenogenital syndrome manifested by pronounced masculinization and hirsutism reacts to her changed appearance with anxiety and depression.

Changes commonly occur in the *skin* of patients with Cushing's or the adrenogenital syndrome. Acne and "coarsening" of the skin are noted in 80 per cent of the latter. About 60 per cent of patients with Cushing's syndrome have acne, some increased pigmental and purple striae, and easy bruising with development of ecchymoses after minor trauma, such as from a blood test. These changes are often striking, particularly the striae, which are variously described as "red," "viola-

ceous," or "purple." They can easily be felt as depressed, small gullies as the examining fingers are passed over them. This thin, easily bruised skin results from the effect of excess cortisol on the proteins in the skin (mobilization of protein for gluconeogenesis plus the "catabolic" effect of glucocorticoids). Rapid gain in weight during pregnancy or from overeating, or rapid development of girls can cause stretching and striae of the skin. Patients with Cushing's syndrome and truly thin skin have a different appearance; their transparent skin reveals the subcutaneous vasculature, and causes plethora in general but especially in the face.

Weakness is a major complaint of 30 per cent of patients with primary aldosteronism and 60 per cent of those with Cushing's syndrome. In the latter patients weakness is due to the catabolic effect of cortisol with muscle wasting, whereas in the former, it is caused by hypokalemia, the weakness often being episodic and paralleling the reduction in serum potassium concentration (weakness is pronounced when the serum potassium concentration is below 3 mEq./L.).

Swelling is a major symptom in about 60 per cent of patients with Cushing's syndrome. Of 35 patients with primary Cushing's syndrome seen at the Ochsner Clinic from 1962 to 1965, 60 per cent had mild or moderate edema. More surprising was the fact that in half of these patients swelling was the initial or an early abnormality.

Osteoporosis is present in 85 per cent of patients with Cushing's syndrome. Although it is a common medical problem, it can be an important diagnostic clue when we realize that 95 per cent of patients with Cushing's syndrome are younger than 60 years of age and 80 per cent younger than 50, age groups uncommonly affected by osteoporosis. Furthermore, 60 per cent have decalcification of the skull and 30 per cent vertebral compression fractures.

Two common laboratory tests yield important clues suggesting Cushing's syndrome: the glucose tolerance test and the eosinophil count. Ninety per cent of patients will have *evidence* of *diabetes* by glucose tolerance test (30 per cent with frank diabetes) and 80 per cent will have low *eosinophil counts* (less than 100/cu. mm.).

Table 2 shows the average reported incidences of the various symptoms in patients with the three hyperfunctioning adrenocortical syndromes. From an analysis of this table, three conclusions can be drawn. First, the cortisol excess of Cushing's syndrome causes many symptoms so that a reasonable rule would be that the patient should have at least three before this possibility is seriously considered. Second, in all hypertensive patients the possibility of primary aldosteronism must be considered. Hypokalemia is always present, but special observation and tests may be required to demonstrate it. Again, only a limited number of patients will require more extensive tests or hormonal assays. Third, hirsutism must be carefully evaluated, but hirsute women who do not have virilism or serious difficulty with menstruation or fertility rarely require further study. Newborn infants and infants whose sex is not certain should have prompt, careful study. Sudden development of hirsutism, especially with sexual development, in childhood is another indication for prompt investigation.

Table 2. *Comparison of the Average Reported Incidences of Symptoms of the Hyperfunctioning Adrenal Syndromes*

MANIFESTATION	CORTISOL EXCESS (CUSHING'S SYNDROME)	ALDOSTERONE EXCESS (PRIMARY HYPERALDOSTERONISM; CONN'S SYNDROME)	ANDROGEN EXCESS (ANDROGENITAL SYNDROME)
	% Pt.	% Pt.	% Pt.
Obesity	97		
Gonadal Disease	85		100
Hirsutism	70		95 (Women)
Hypertension	85	100	
Weakness	60	30	
Mental	65		
Cutaneous	80		
Swelling	60		
Osteoporosis	84		
Diabetes	90		
Low eosinophil count	80		
Low potassium	10	100	
High sodium	Rare	10	

ETIOLOGY OF HYPERFUNCTIONING ADRENAL CORTEX

The pathophysiologic changes of the hyperfunctioning adrenal cortex are due to excessive production of steroids. This accounts for almost all the manifestations of adrenal disease, symptoms from damage by actual physical distortion of the local tissue by adrenal hyperplasia or functioning tumors being rare. Hyperplasia accounts for 60 to 80 per cent of cases in reported series;[13, 15] enlargement is usually slight (one and one-half to four times heavier than the normal 4 to 12 gm.). In about 10 per cent of reported cases no gross enlargement was noted at necropsy or operation even though hyperfunctioning was proved. The 15 to 30 per cent of patients with tumors had chiefly benign adenomas, but approximately one-fourth had malignant lesions. The clinical picture produced by hyperplastic glands is similar to that produced by tumors except that in patients with tumors, and more commonly malignant ones, the duration is shorter from onset of symptoms to establishment of diagnosis (6 to 12 months) than in patients with hyperplasia (1.5 to 3 years).

The underlying cause of excessive production of one or more adrenal steroids in adrenocortical diseases varies. Tumors occur in from 15 to 30 per cent of patients with Cushing's syndrome (usually 75 per cent are benign and 25 per cent malignant.[5] Overproduction of steroids in these patients presumably is the result of the autonomous behavior of the tumor. In 70 per cent or more of patients the adrenal pathologic changes consist in bilateral hyperplasia and hyperfunction, but the source of this stimulation of the adrenals is not known. Excessive production of endogenous ACTH seems highly probable, yet its cause has defied explanation. Although at postmortem examination more than 50 per cent of the patients with adrenal hyperplasia have been found to have pitui-

tary tumors, often basophilic, these tumors are usually small, and only 3 to 5 per cent of patients with Cushing's disease have enlarged sellas. Much evidence has been gathered to indicate that the level of corticotrophin (ACTH) in the blood is abnormally high in patients with adrenal hyperplasia, both with and without pituitary tumors. Although neurohormones from the hypothalamus are known to stimulate the pituitary to release ACTH, gross pathologic changes in the hypothalamus of patients with Cushing's syndrome have been rarely described, and documentation of microscopic pathologic changes in the hypothalamus with or without excessive production of neurohormones must await development of adequate techniques.

During the past ten years it has been established that nonendocrine tumors can stimulate the adrenal glands.[14] These growths, almost always malignant, have been found chiefly in the lung (oat cell carcinoma), but they have also been reported in the thymus, pancreas, and gallbladder. Presumably, these tumors stimulate the adrenals through production of adrenocorticotropin-like material.

Hyperfunctioning of the pituitary in patients with adrenogenital syndrome can be explained by failure of adrenal glands to produce amounts of cortisol adequate to normally suppress production of ACTH. These patients have an enzymatic defect in steroidogenesis; the most common failure appearing at 21-hydroxylation so that 17-hydroxyprogesterone cannot be converted to cortisol, as is indicated in Figure 1, where the site of action of the 21-hydroxylating enzyme is shown. Cortisol is the only normally produced adrenal steroid that inhibits production of adrenocorticotropic hormone (ACTH), which is one of the mechanisms of ACTH secretion control ("servomechanism"). The high ACTH level continuously stimulates the adrenals so that large amounts of 17-hydroxyprogesterone (or closely related steroids) are secreted and these are androgenic. Although these steroids are weak androgens, they may be produced at rates as high as 100 mg. daily, amounts comparable in masculinizing effectiveness to the daily secretion by normal men of testosterone, which is sixty times as potent. Obviously, endogenous ACTH is causing the pathologic overactivity in the usual adrenogenital syndrome. The clinical picture in the child with the adrenogenital syndrome varies because the enzyme deficiencies blocking cortisol production are usually incomplete. In approximately one-third of these children the block is severe enough to prevent adequate output of cortisol or aldosterone and thus cause serious loss of sodium, and the general picture of hypo-adrenalism will appear, especially in times of stress when all mammals need greatly increased amounts of both mineralosteroids and glucosteroids. In more than 95 per cent of patients with primary (hyper) aldosteronism a small, benign, adrenal tumor has been found; again, autonomous behavior of these tumors is presumed to account for the excessive production of aldosterone.

Only the spontaneous diseases caused by excessive adrenocortical hormones are rare. The widespread use of adrenal steroids and corticotropin (ACTH) has made iatrogenic Cushing's syndrome extremely common. Use of corticosteroids or ACTH for more than two weeks en-

tails the risk of development of this untoward reaction as well as leaving the patient particularly vulnerable to development of adrenocortical deficiency in times of stress—especially surgical—for months after discontinuance of treatment. A number of drugs often cause hirsutism and masculinization.

STEROID ASSAYS AND SPECIAL PROCEDURES

Although no simple screening hormonal assays for establishing a diagnosis of adrenocortical hyperfunctioning disease are available, the diagnosis can be made with reasonable certainty. The ideal test would be one demonstrating hyperproduction (with the patient in a resting state) of a specific adrenal steroid, cortisol, in Cushing's syndrome and of aldosterone in primary aldosteronism. Such procedures are available, usually done with isotope dilution techniques, but they are still in the developmental stage and are available in only a few medical centers.

Because different methods are used in different laboratories, the normal range of assay values must be established for each laboratory, and the physician using a particular laboratory must know them. These values should be adjusted to age and sex and sometimes are reported as related to body surface area or are expressed per kilograms of body weight or per gram of 24-hour urinary creatinine. To give some indication of the adrenocortical activity some average values are listed.

Cortisol plasma levels range from 10 to 20 mcg./100 ml. plasma and 17-hydroxysteroid 24-hour urine levels from 2 to 10 mg./24 hours, and cortisol secretory rate from 10 to 20 mg./24 hours.

Normal aldosterone values are about one-twentieth this level: 100 to 200 mcg./24 hours secretory rate and 100 mcg./24 hours urinary excretion. These low values create technical difficulties in procedures and make the normal blood levels so low that accurate measurement is impossible.

Androgen is secreted by the adrenals and gonads and no simple procedure can differentiate between these two sources. Their excretion products in urine are measured chemically by methods combining many steroids. Usually the method involves determination of 17-ketosteroids, which vary widely with age and sex.

DIFFERENTIAL DIAGNOSIS

Cushing's Syndrome

Because treatment of Cushing's syndrome is formidable, the physician must be certain in making this diagnosis. Detailed discussion of the problems involved is not appropriate here, but some observations are pertinent. Although the final diagnosis will depend on hormonal assays demonstrating excessive production of 17-hydroxycorticosteroid, the importance of seriously considering Cushing's syndrome only in patients who have many of the clinical manifestations suggesting the disease should be emphasized. Nugent and associates[12] reported that, of 211 patients suspected of having the disease, the diagnosis was accurately made by use of the probability theory of analysis only of symptoms and

signs in 50 per cent, whereas a single steroid assay screening test did not yield that level of accuracy.[12] Their study also demonstrated that, of 211 suspects, only 20 were finally proved to have Cushing's syndrome.

Suitable hormonal assay can be performed, as 17-hydroxycorticosteroid plasma level, 17-hydroxycorticosteroid 24-hour urinary excretion determination, or 24-hour cortisol secretion rate. Usually, it will be necessary to determine the effect on assay values of stimulation or suppression tests or variations produced by altering the time of day collections are made. Table 3 shows these variations in normal persons, as well as patients with Cushing's syndrome produced by different pathologic changes with the values of 24-hour urinary excretion of 17-hydroxysteroid (given in the numbers under the arrows). The baseline values of 24-hour urine excretion are elevated in probably more than 90 per cent of patients with Cushing's disease, but 5 to 10 per cent of patients eventually "proved" to have the disease may not have it. In these, proof may come only after continuing observation, retesting, and evaluation of the various tests listed so that strong clinical suspicion cannot be ignored if only a single hormonal assay yields a nearly normal result.

Probably the most difficult patients to evaluate for possible serious adrenal overproduction are those with obesity, hypertension, and diabetic glucose tolerance curves who have mildly elevated 17-hydroxycorticosteroid levels. About 1 to 5 per cent of obese patients studied have shown mild elevation.[1] These patients can be differentiated from those

Table 3. *Differential Diagnosis of Cushing's Syndrome*

Ancillary Clues	Diseases	Baseline (Must be resting and no stress)	Diurnal Variation		Stimulation ACTH Test		Suppression Test Dexamethasone				
							2 mg./day		8 mg./day		
			8 A.M.	4 P.M.	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 3
	Normal Males and Females	N 2–10	N 8	↓ 4	↑ 20	↑ 30	↓ 1–5	↓ 0–3	↓ 0–1	↓ 0–1	↓ 0–1
	Obesity (1–5% of obese pt.)	↑ 12–18	↑ 11	↓ 6			↓ 6	↓ 3			
Enlarged Sella Turcica	Cushing's Syndrome Pituitary 2–5% of pt.	↑ to ↑ 15–30	↑ 25	↑ 25	↑ 25	↑ 30	↑ 25	↑ 25	↑ 25	↑ 25	↑ 25
	Hyperplasia 70% of pt.	↑ to ↑ 20–30	↑ 25	↑ 25	↑ 35–60	↑ 40–70	↑ 15	↑ 12	↓ 8	↓ 4	↓ 4
	Tumors Adenoma 20% of pt.	↑ 25–40	↑ 40	↑ 40	↑ 40	↑ 40	↑ 40	↑ 40	↑ 40	↑ 40	↑ 40
	Carcinoma 5% of pt.	↑ 50–80	↑ 55	↑ 55	↑ 55	↑ 55	↑ 55	↑ 55	↑ 55	↑ 55	↑ 55
Evidence of Cancer in Lung, Thymus, Gallbladder, etc.	ACTH from Nonendocrine Tumors	↑ 30–80	↑ 40	↑ 40							
History	Iatrogenic Cushing's Syndrome	↑ to ↑ 20–60	↑ 35	↑ 35							

N = Normal ↓ = Decrease ↑ = Moderate Excess ↑ = Great Excess ▨ = Important Clues

20 – 60 = Representative Values

Table 4. *Endocrine Studies Necessary to Diagnose Cushing's Disease*

DAY	ENDOCRINE TESTS	OTHER TESTS
1	Two 12 hour urine, for diurnal rhythm check 7 A.M.–P.M., 7 A.M.–P.M.	Skull x-ray Absolute eosinophil count
2	Same as 1st day plus plasma level corticosteroid	0
3	ACTH, 25 units IV, for 8 hours Simultaneous start of 24-hour urine	Absolute eosinophil count
4	Same as 3rd day	Same as 3rd
5	Baseline 24-hour urine collected for 17-hydroxycorticosterone	
6	Dexamethasone 0.5 mg. every 6 hours. Start 24-hour urine for 17-hydroxycorticosterone	Glucose tolerance test
7	Same as 6th day	
8	Dexamethasone 2 mg. every 6 hours. 24-hour urine for 17-hydroxycorticosterone	
9	Same as 8th day	
10	Same as 8th day	

with Cushing's syndrome because they react, as do normal people, in two ways.

First, normal persons show diurnal variation in steroid excretion (one of many biologic phenomena showing changes—circadian rhythm). The highest cortisol blood level is at approximately 8:00 A.M. (or largest 17-hydroxycorticosteroid excretion 7:00 A.M. to 7:00 P.M.) and lowest in late afternoon. Therefore, usually 4:00 P.M. blood level is compared (or 7:00 P.M. to 7:00 A.M. 17-hydroxycorticosteroid excretion). The normal and the obese patient without Cushing's syndrome will have only one-half the value at these times (8:00 A.M. cortisol 8 mg./100 ml. blood versus 4:00 P.M. cortisol of 4 mg.).

Secondly, the obese patient responds as does the normal with full suppression of ACTH to small amounts of dexamethasone—a *synthetic corticosteroid.* Whereas the natural steroid, cortisol, will suppress ACTH production only when given in amounts of 20 to 30 mg./24 hours, dexamethasone will suppress ACTH when given in a dosage of only 2 mg./24 hours. This small amount will contribute only a fraction (1/10) to cortisol blood levels or 17-hydroxycorticosteroid excretion levels so that measurements of these will be reduced to only one-tenth of normal in normal persons or obese patients without Cushing's syndrome. A few obese patients will show some slowness of suppression to dexamethasone, but continuing observation will differentiate them from the Cushing's patient as their increase in 17-hydroxycorticosteroid values

are only slightly higher than normal and return to normal values as they lose weight.

In the patient with Cushing's syndrome whose cortisol excess is caused by adrenal hyperplasia, suppression will occur at levels of 8 mg./day, whereas adrenal tumors causing Cushing's syndrome will not do this. Therefore, the suppression test is usually a vital necessity in the evaluation of patients. Furthermore, stimulation by ACTH greatly increases secretion of cortisol in normal persons and patients with adrenal hyperplasia, but not in those with tumors. Table 4 recapitulates the endocrine studies necessary to evaluate a patient suspected of having Cushing's syndrome. This formidable study is best undertaken in a hospital.

Primary Hyperaldosteronism

Physicians must now consider primary aldosteronism, as well as the other curable causes of hypertension, in all patients with high blood pressure. Demonstration of primary aldosteronism is not difficult in most patients with the disease. Investigation of hypertension requires a definite plan of study that should include repeated blood pressure determinations, electrocardiography, blood urea nitrogen determinations, CO_2, serum sodium, potassium and chloride determinations, roentgenography of the chest (with lateral view), and roentgenography of the kidneys, ureters, and bladder, and often renal studies which may include intravenous pyelography and Addis count clearance.[9] The classification of hypertensive disease shown in Table 5 indicates what an adequate approach to thorough evaluation of this common problem must entail. Our concern is with the adrenal cortex since comments on the patient with Cushing's syndrome have already been made in the preceding section. Differentiation between Cushing's syndrome and primary aldosteronism is not difficult and is made on the basis of hor-

Table 5. *Classification of Hypertensive Disease*

1. Humoral
   - A. Adrenal cortex
     1. Cushing's syndrome
     2. Primary aldosteronism
   - B. Adrenal medulla
     1. Pheochromocytoma
   - C. Renal
     1. Bilateral renal disease
     2. Unilateral renal disease

2. Neurogenic
   - A. Essential hypertension
     1. Normotensive hyper-reactor
     2. Intermittent hypertension
     3. Continuous hypertension
   - B. Malignant

3. Mechanical
   - A. Coarctation of aorta

Table 6. *Diseases Causing Hypokalemia and Hypertension*

1. Primary aldosteronism (edema rare)
   - A. Tumor. Benign single adenoma in 95% of reported cases.
   - B. Adrenal hyperplasia. Very rare.

2. Secondary aldosteronism (edema *common*)
   - A. Malignant hypertension
   - B. Bilateral or unilateral renal disease

   Mechanism producing aldosterone secretion:
   Renal ischemia causing decrease in functioning vascular volume in kidney juxtaglomerular apparatus, producing:
   Renin—reacts with angiotensinogen (produced by liver) creating
   Angiotensin—potent vasopressor by arteriole smooth muscle stimulation causing general body circulating volume loss which induces
   Aldosterone secretion

3. Renal potassium loss
   - A. Diuretic therapy (iatrogenic potassium loss)
   - B. Potassium-wasting renal disease

   Chronic pyelonephritis
   Chronic nephritis (advanced stage)
   Fanconi syndrome
   Renal tubular acidosis

4. Cushing's syndrome (10 to 15 per cent with low serum potassium)
   - A. Adrenal
     1. Hyperplasia
     2. Tumor—adenoma
   - B. Pituitary tumor

     ACTH producing
   - C. Extra-adrenal or gonadal cancer

     ACTH-like substances reported produced by lung, thymus, pancreas, and gallbladder

5. Miscellaneous group (all rare)
   - A. Heavy chronic licorice ingestion

     Glycyrrhizinic acid from licorice causes potassium loss and sodium retention (probably due to its conversion to a deoxycorticosterone-like substance—probably in liver)
   - B. Familial renal disorder causing potassium loss

mone secretion studies. In primary aldosterone the 17-hydroxycorticosteroid excretion will always be normal and aldosterone secretion elevated whereas in Cushing's syndrome the 17-hydroxycorticosteroid excretion is always increased. The aldosterone secretion may also be elevated in a small number of proved cases of Cushing's syndrome; this presents no problems in diagnosis since the excess cortisol effects dominate the clinical picture, and treatment is the same.

The most important clue suggesting primary hyperaldosteronism as the cause of hypertension is the almost invariable appearance of hypokalemia. Although the patient with primary aldosteronism is rarely asymptomatic, the only abnormal sign being hypertension, which is usually about 170/100, the common associated symptoms of primary aldosteronism are muscle weakness (due to the hypokalemia) plus polyuria and headaches. An important clue may be development of weakness during the first week of thiazide therapy as the result of rapidly developing hypokalemia. The diseases causing hypertension and hypokalemia are listed in Table 6.

The greatest difficulty in differential diagnosis is in distinguishing between primary and secondary aldosteronism. The fully developed disease is not difficult to recognize. Hypokalemia must be present to make the diagnosis in these patients, but recent case reports indicate that low potassium concentration may be mild or intermittent.[3] Since single demonstration of normal serum potassium concentration cannot exclude the diagnosis, the hypertensive patient with borderline values should be given a simple screening test. In this test, after discontinuance of all medication, the patient is given 200 mEq. of sodium a day (which is five times the normal 40 mEq. of salt intake) for seven days, and the serum potassium concentration is determined daily for the last three days.

Since sodium loading at this level in a normal person greatly reduces aldosterone production and no exchange of sodium for potassium in the distal tubule will occur, hypokalemia will not develop. In the patient with the autonomously functioning adrenal aldosteronoma, the aldosterone excess will continue, large amounts of potassium will be lost in the urine, and serum potassium will drop to 3.2 mEq. and usually lower. The patient with aldosteronism secondary to renal disease often will have low serum potassium concentration along with excess aldosterone secretion, but in contrast to the patient with primary aldosteronism, who has hypernatremia, hypervolemia, and alkalosis, the patient with secondary aldosteronism has hyponatremia, hypovolemia, and acidosis. These differences are so great that differentiation is not difficult. Obviously, primary aldosteronism, if allowed to continue, eventually can seriously damage the kidneys so that secondary aldosteronism can be superimposed on the primary process, but unfortunately for the patient the question usually will then be nearly academic.

Excessive secretion of aldosterone usually is demonstrated by determinations of 24-hour urinary excretion of aldosterone or of the secretory rate, since the plasma levels of aldosterone are so low (in the range of 0.011 to 0.024 μg/100 ml. plasma) that no practical clinical methods are available. The 24-hour urinary values normally range from 5 to 15 μg. during normal salt intake. Unfortunately, about 10 per cent of patients with surgically proved aldosteronoma have had repeated normal urinary excretion rates but have shown elevated secretory rates. The secretory rate of aldosterone can be determined by using radioisotope labeled (^{14}C) aldosterone, the normal value being 150 mg./day; 100 to 200 mg./day is the range with normal sodium uptake of 5 gm. day. The test is exacting and rather expensive to perform but should be done if clinical evidence suggests this disease and the 24-hour urine values are only slightly elevated.

Adrenogenital Syndrome

Most cases of adrenogenital syndrome will be discovered at birth or during infancy, since overproduction of androgens by the adrenal glands is an apparently inherited deficiency of steroidogenesis. The defect apparently may be latent, however, since onset of hirsutism and virilism has been observed later in childhood or after puberty.[8] The

Table 7. *Classification of Hirsutism in Women*

% of Pt in Category with Elevated 17 KS	Urinary Excretion: Pregnanetriol	Urinary Excretion: 17 KS	Disease	Estimated % of Pt with Disease having: Hirsutism	Estimated % of Pt with Disease having: Virilism	Estimated % of Hirsute Females with Disease
	N 0.2 - 0.5 N 0.0 - 0.2 N 0.2 - 0.5 N 0.5 - 1.5	N 2.0 - 5.0 N 0.2 - 2.0 N 2.0 - 7.0 N 5.0 - 15.0	Normal Females Newborn - 3 wk 3 wk - 5 yr 6 yr - 15 yr > 15 yr			
100	↑↑ 3 - 20	↑↑ 20 - 150	Adrenogenital Syndrome	100	100	0.5
			Cushing's Syndrome			
5	↑ 1 - 5	↑ 20 - 60	a. Adrenocortical Hyperplasia	60	5	0.3
15	↑ 3 - 10	↑ 40 - 150	b. Adrenocortical Tumor	75	15	0.1
			Ovarian Tumors			
95	N (Rare elevation)	↑↑ 20 - 150	a. Arrhenoblastoma	100	100	0.02
			b. Adrenal Rest Tumor	100	100	0.02
			c. Thecoma	100	100	0.001
90		↑ 20 - 75	Iatrogenic Androgen Therapy	100	50	3.0 - 5.0
			"Idiopathic Hirsutism"			
0	N	N	a. "True Idiopathic" (Racial, Genetic, etc.)	100	0	90.0 - 95.0
5 - 20		↑ 18 - 30	b. Stein-Leventhal Syndrome (Polycystic Ovary Syndrome)	70	5 - 10	2.0
100		↑ 18 - 30	c. "Borderline" Adrenogenital Syndrome	90	75	2.0

17 KS = 17-ketosteroids N = Normal ↑ = Moderate Excess ↑↑ = Great Excess 20 - 60 = Representative Values

explanation for delay in appearance of manifestations in this "acquired" form of adrenal virilism is not known.

Recognition of the adrenogenital syndrome in adults is basically a problem of discovering the cause of hirsutism in women. Classification of the causes of hirsutism (Table 7) will give perspective to the problems faced. In this classification, adrenogenital syndrome has been used to designate the disease, involving only the enzymatic defect of steroidogenesis in which production of cortisol is blocked so that androgenic steroids appear in excess. This can be confusing, because some authors include under this designation all diseases of adrenal origin that produce predominantly clinical virilization; such a definition includes this enzymatic defect, as well as adrenal tumors that cause severe masculinization and Cushing's syndrome with pronounced masculinization.

In the investigation of hirsute women, the need for hormonal assays or other special studies can be eliminated in more than 90 per cent after careful physical examination and history taking. In newborn infants and early childhood, hirsutism from the adrenogenital syndrome or the even rarer adrenal or gonadal virilizing tumors invariably appears with masculinization. Newborn girls have ambiguous external genitalia. Genital abnormalities in the newborn require careful study, starting

with sex chromatin determination, because severe failure of steroid formation starting in the fetus may cause masculinization in an infant who may be mistaken for a male with hypospadias and cryptorchidism. Obviously, with an incidence of only 1 in 5000 births, severe adrenogenital syndrome in newborns is much less common than hypospadias, but careful evaluation of each individual and consideration of this possibility must be the rule.

In obtaining the history, the physician should find out when the hirsutism was first noted. Most hirsute female patients have a genetic predisposition, and the overgrowth of hair is not due to disease. About 10 per cent of patients, however, will report abrupt change in the pattern and rate of growth during a period of one to twelve months. In older or married women with severe endocrine disease, histories will reveal serious abnormalities, such as amenorrhea, oligomenorrhea, abortions, or sterility in 90 per cent.

During physical examination, the physician should note the degree and distribution of the hirsutism and should look for the following signs of virilization: recession of hair at scalp and temple, enlargement of clitoris (more than 1.5 cm.), regression of size of breasts, changes of body habitus or musculature toward masculinity, and lowering of pitch of voice.

One or more of these signs are strong evidence of excessive production of androgen, and careful search for the source is indicated. Unfortunately, these signs are not pathognomonic of pathologic levels of androgenic steroid, since individual variation of the pilary apparatus to hormonal stimulation suggests that a minority of women, racial and familial factors aside, seem to have hair follicles that have growth responses to low levels of androgens.

Drugs and Other Agents Inducing Hirsutism

In obtaining the history, the physician should ask the patient if she has been taking any drugs, since certain drugs can produce hirsutism with and without virilization.[8]

WITH VIRILIZATION. Norethindrone (Norlutin), norethynodrel (Enovid), and other synthetic progestational drugs cause hirsutism with virilization in only a small number of female patients, but because these drugs are frequently prescribed, they have become an important cause of hirsutism. Presumably some unusual event in steroidometabolism causes this small number of persons to convert these particular molecules to ones with androgenic tendency.

Severe hirsutism and virilization have been reported to develop as a result of treatment with anabolic steroids (stanalone, methandriol, androstalone, and 19-nortestosterone). To date, all of these steroids have been reported to have detectable androgenic effects.

Susceptibility to the androgenic effects varies widely in female patients. The physician who prescribes anabolic steroids must observe the patient closely to detect these undesirable side effects at the earliest time.

"Shot-gun" remedies incorporate androgenic hormones mixed with

other hormones, vitamins, minerals, and tranquilizers. These drugs should *never* be prescribed.

In women treated with androgens, iatrogenic virilization is inevitable. The time of its appearance depends on individual sensitivity, dosage, and duration of treatment. Ratios of combinations of estrogens and androgens have been proposed, but the ideal ratio which would insure prevention of undesired effects is not known. In most cases, their use has no definite advantage and it is impossible to predict the individual women's susceptibility to virilization.

WITHOUT VIRILIZATION. The occasional appearance of hypertrichosis after use of streptomycin and diphenylhydantoin has been reported. Excessive growth of hair has been noted after treatment not using drugs, as for example, after plaster casts or roentgen therapy. These reports of development of hypertrichosis after varied agents emphasize how poor our basic understanding of the physiology of the hair follicle is and its response to various factors. The term "congenitally sensitive hair follicles" describes, but does not explain, what is often observed.

HORMONAL ASSAY. The hormonal assay usually available for estimation of androgenic steroid production is the 17-ketosteroid 24-hour urine determination. The normal range for women is 5 to 15 mg./day. Adults with the acquired adrenogenital syndrome usually have values ranging from 25 to 100 mg./day. Ovarian tumors (arrhenoblastoma or adrenal rest tumors) usually are masculinizing. They produce variable values ranging from slightly elevated to extremely high (15 to 200 mg./day). Therefore, finding an ovarian mass (usually moderate to large size) indicates the source of the androgen rather than the hormonal values. Another important finding on hormonal assay (high normal for women, 1.5 mg./day) in patients with the adrenogenital syndrome is pregnanetriol values of 2.5 to 10 mg./day. Also, pregnanetriol is usually elevated in patients with ovarian tumors or Cushing's syndrome with symptomatic androgenic steroid production. Patients with Cushing's syndrome (ranging from 5 to 20 per cent) have significant androgen excretion (highest percentages in patients with adrenal tumors), so that the hirsutism and virilization may dominate the clinical picture. Patients with Cushing's syndrome can be differentiated from *all* other patients with hirsutism on the basis of hormonal assays, since *only* patients with Cushing's syndrome have elevated 17-hydroxycorticosteroid excretion along with elevated 17-ketosteroids. *Both* of these levels should be determined in the initial investigation of patients suspected of having Cushing's syndrome or virilization.

About 5 per cent of women with hirsutism who do not have Cushing's or adrenogenital syndrome have elevated androgen levels.[4] Their problem is still only imperfectly understood, but reasonable approaches for investigation and treatment can be outlined. Their diseases may be classified into three groups: polycystic ovarian syndrome (Stein-Leventhal syndrome), borderline adrenal dysfunction, and Achard-Thiers syndrome (obesity-diabetes-hirsutism).

Table 8 shows the responses of hirsute patients with elevated androgens to various suppression and stimulation tests that will help clarify their sources of excessive androgen. The adrenogenital syndrome can be differentiated from Cushing's syndrome with virilization by demonstration of rapid suppression of excess androgen to small dosage of dexamethasone (2 mg./day) in adrenogenital patients, in contrast to a much larger dosage (8 mg./day) needed to suppress excess androgen in patients in whom Cushing's syndrome is due to adrenal hyperplasia; in patients with adrenal tumors suppression does not occur at any dose. The basic difference between the two, it should be recalled, is the increased 17-hydroxycorticosteroid in patients with Cushing's syndrome, which does not occur in patients with adrenogenital syndrome.

More difficult to evaluate are the patients with "borderline adrenogenital syndrome" and those with polycystic ovaries (Stein-Leventhal syndrome). In all the former type and in many of the latter, 17-ketosteroid 24-hour excretion rate will be moderately elevated (16 to 25 mg./24 hours), whereas elevation in the adult with adrenogenital syndrome usually is much higher (above 25 mg./24 hours). These groups differ chiefly in the elevation of androgen by gonadotrophin administration in patients with polycystic ovaries (Table 8). Treatment with corticosteroids can be tried, and wedge resection of the ovaries in the patients with polycystic ovaries usually improves their problem, but evaluation of these patients is not simple. Physicians interested in these problems are referred to recent published reports.[4, 6, 10, 11] Physicians should guard against a too optimistic prognosis regarding the hirsutism, since once stimulated, hair follicles continue to grow rather vigorously after cessation of the stimulation.[7, 11]

Table 8. *Suppression and Stimulation Responses in Hirsutism*

Disease	Baseline	Suppression Test: Dexamethasone 2 mg./day 2 Days	Suppression Test: Dexamethasone 8 mg./day 2 Days	Suppression Test: Estrogen for 7 Days	Stimulation Test: ACTH for 2 Days	Stimulation Test: Gonadotrophin for 2 Days
Adrenogenital Syndrome	↑	↓	↓	↑	⇑	↑
"Borderline" Adrenogenital Syndrome	↑	↓		↑	⇑	↑
Stein-Leventhal Syndrome (Polycystic Ovary Syndrome)	↑	↑-↓		↓	↑	⇑
Normal Females	N	↓		↓	↑	N
Cushing's Syndrome						
a Adrenocortical Hyperplasia (5% of pt)	↑	↑	↓		⇑	
b Adrenocortical Tumor (15% of pt)	⇑	⇑	⇑		⇑	
Ovarian Tumors	↑	↑	↑		↑	↑-⇑

N = Normal ↓ = Decrease ↑ = Moderate Excess ⇑ = Great Excess ▨ = Important Clues

SUMMARY

Systematic analysis of clinical manifestations in hyperfunctioning adrenocortical diseases demonstrates that these rare syndromes are manifested by common complaints. It also reveals clues that can greatly reduce the number of patients requiring adrenal hormonal assay.

Patients with Cushing's syndrome have numerous complaints (weakness, obesity, diabetic tendency, thin skin with striae and bruisability, hypertension, hirsutism, and psychic problems). Patients with aldosteronism invariably have hypertension accompanied by hypokalemia but relatively few other symptoms. The common problem of hirsutism in women can be caused by the rare adrenogenital syndrome but invariably is accompanied by other gonadal disturbances with virilization.

The excessive production of cortisol-like steroids in 70 per cent of patients with Cushing's syndrome comes from unphysiologic hyperplasia and hyperfunctioning due to excess corticotropin (ACTH) usually of undetermined origin, but ACTH can arise from pituitary tumors or nonendocrine cancer. Adrenal tumors produce excess steroids because of their autonomous behavior. In the adrenogenital syndrome excessive production of androgens appears because continuous endogenous corticotropin stimulation comes from an inherited enzymatic defect in adrenals causing failure to produce adequate cortisol, which normally inhibits corticotropin secretion.

Establishment of a diagnosis of Cushing's syndrome requires lengthy study aimed at documenting production of cortisol above the normal secretory rate of 10 to 20 mg./day.

All hypertensive patients require careful evaluation to discover the 10 to 20 per cent with curable disease including primary aldosteronism. Excess aldosterone causes hypokalemia, which is important to demonstrate through appropriate studies including salt-loading tests. The diagnosis is established by demonstrating a secretory rate of aldosterone above the normal 100 to 200 mcg./24 hours.

Patients with the adrenogenital syndrome have excessive production of 17-ketosteroids, which are weak androgens. They secrete these in very large amounts. Urinary excretion above the normal 1.5 mg./24 hours and its suppression to normal by physiologic doses of cortisol establishes the diagnosis in infants and children younger than five years with gonadal abnormality and hirsutism. One-third of these infants and children will have decrease in cortisol production severe enough to produce the "salt-losing syndrome" and have dangerously or fatally low levels of cortisol production during periods of stress. Women with delayed onset of adrenogenital syndrome will be recognized among the large number of women with hirsutism by clinical signs of virilization. The urinary excretion of 17-ketosteroid in these women is usually 150 per cent or more above the high normal of 15 mg./24 hr. This rate and the clinical symptoms and appearance return to normal with physiologic doses of cortisol.

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Steroid Synthesis by the Human Ovary: A Compartmental Viewpoint

BERNARD F. RICE, M.D.

Since manifestations of gonadal disorders of steroid metabolism generally have rational explanations, they should not, in my opinion, be classified as "unusual." An attempt will be made to provide a reasonable framework of reference for the practicing physician so that he may properly interpret "unusual" clinical manifestations of gonadal disorders and hopefully remove them from that category.

GENERAL PATHWAYS OF STEROIDOGENESIS

Figure 1 shows the structural formulas of the major steroids and the *general* pathways of biosynthesis for these steroids. Although there are certain similarities in the pathways of steroid biosynthesis in all human gonadal tissues, differences reside in the gonads which allow for greater or lesser amounts of a given steroid to be secreted. The biochemist is likely to interpret the quantitative differences in the secretory product of the gonads as simply reflecting differing concentrations of enzymes within the gonad; that is, the major secretory product of the testis is testosterone because there is a relative deficiency of the enzyme necessary for aromatization of testosterone to estradiol-17β (Fig. 1,*f*). A rate limiting enzymatic step of this type in the testis is considered "normal." If, however, one finds that an androgen, such as Δ^4-androsterone-3,17-dione, is the major secretory product of an ovary, this is often considered "abnormal" and representative of a biochemical defect in aromatization (Fig. 1,*f*). Similarly, production of progesterone by the human corpus luteum *could* be considered "abnormal" and due to a defect in 17-hydroxylation of progesterone (Fig. 1,*d*) resulting in lesser quantities of C-21 and C-19 "precursor" steroids available for estrogen synthesis, if one assumes that the major secretory product of an ovary should be an estrogenic steroid.

From the Department of Internal Medicine, Ochsner Clinic, New Orleans, Louisiana

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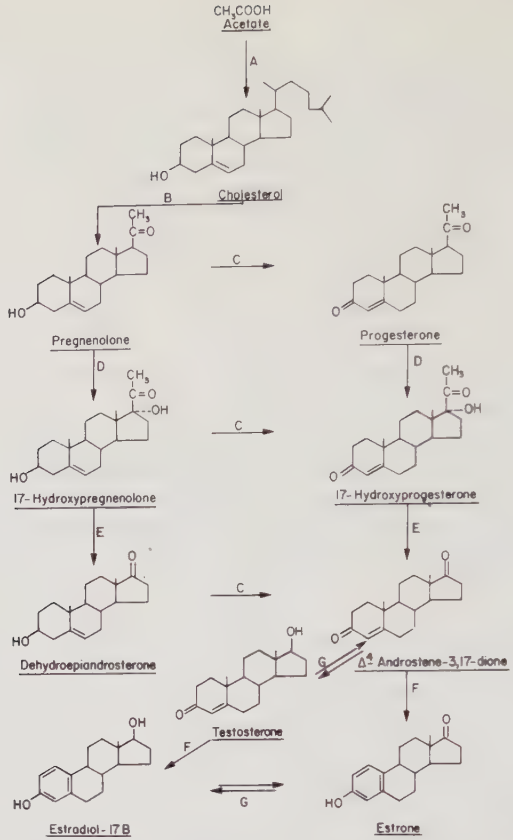

Figure 1. General pathways of steroid biosynthesis in human gonadal tissue. *A*, Formation of cholesterol (C_{27} compound) from acetate. *B*, Cleavage of the cholesterol side chain to yield C_{21} compound. *C*, 3β-ol-dehydrogenase and Δ^4-Δ^5-isomerase reaction which yields Δ^4-3-keto steroids. *D*, 17α-hydroxylation. *E*, Cleavage of C_{21} side chain to yield C_{19} steroids. *F*, Aromatization of C_{19} steroids to form estrogens (C_{18} compounds). *G*, 17β-ol-dehydrogenase. (From Ryan and Smith.[11])

A decision regarding whether a steroidal product of a gonad is "normal" or "abnormal" has generally been based on certain prejudice and general lack of information concerning what constitutes normalcy. Unfortunately, considerably more information is available on pathologic states affecting the gonads than on states of testicular and ovarian function during health. Similarly, little attention has been paid to fundamental biologic similarities between the gonads. The experimental endocrinologist and embryologist have long been aware of certain similarities because of morphologic and developmental similarities seen in the gonads of experimental animals. Unfortunately, in the human, the morphologic similarities are usually not apparent by conventional techniques, so that use of biochemical techniques is mandatory for a rational understanding of normal and morbid physiology of the gonads.

THE GONADAL COMPARTMENTS

Methods of Study

The human ovary can be dissected into three reasonably distinct anatomic compartments: the Graafian follicle, the corpus luteum, and the remaining nongerminal elements of the ovary, which will be referred to as the ovarian stroma or interstitium. Although some measurements have been made, available knowledge about the total steroidal product of these different steroid-producing anatomic compartments is limited because of the difficulty of isolating small amounts of native steroidal hormones from the tissue.[12] Since the biologic activity of the different steroids varies widely, interpretation of the tissue concentrations of steroids is also difficult. For example, milligram amounts of progesterone are necessary for a "progestational" effect whereas only microgram amounts of estradiol-17β are necessary to produce an "estrogenic" effect. Ideally, one would desire to have a measure of the *in vivo* production of steroids by *each* individual compartment, since endocrine tissues are "factories" and not "storehouses." At the present time, our methodology permits only assessments of production rates of steroids within the whole organism and gives little information concerning the compartmental *source* of the hormones measured. Use of *in vitro* techniques has enabled investigators to work with small amounts of endocrine tissues and localize possible sources of the steroid hormones which are being measured by *in vivo* techniques.

The ideal system for *in vivo* measurement of production of steroids by individual compartments of the gonads has not been devised. Certain assumptions are therefore necessary for interpretation of data determined by *in vitro* experiments. Interpretation of the data to be reviewed in this presentation assumes that the major radioactive steroids formed *in vitro* from *radioactive acetate* by surviving slices of gonadal tissues are identical to the major secretory product of that gonadal compartment. When tested experimentally, by simultaneous measurements of steroid secretion *in vivo* (spermatic vein blood) and radioactive steroid synthesis from acetate-1-^{14}C *in vitro* (by testis slices), this assumption has been found to be valid.[7] Unfortunately, measurements of this type have been infrequent and difficult to obtain, since it is often more feasible to measure large numbers of radioactive steroids after *in vitro* studies, whereas only a single steroid or at best several steroids are generally measured in laboratories in which *in vivo* techniques are used. Complete analysis of a large group of radioactive steroids formed *in vitro* from acetate-1-^{14}C by a single gonadal tissue requires months of work in a steroid laboratory to obtain valid data. *In vivo* measurements, although of great clinical interest, require less time generally, but are limited by problems of sensitivity, specificity, and reproducibility since only submicrogram amounts of steroid are available for measurement. There is, at best, only a small number of laboratories in the world capable of accurately measuring one or two important gonadal steroids in human plasma.

Currently, valuable and reproducible data appear to have been accumulated by means of the *in vitro* technique of incubating surviving slices of gonadal tissues with radioactive acetate. The radioactive steroids formed are usually purified by a quantitative reverse isotope dilution technique. Nonradioactive steroid carriers are added, the steroid extract is purified extensively, and the radioactivity associated with each carrier steroid is measured. The steroids formed from radioactive acetate do not appear to change with the time of incubation, and the steroids formed *in vitro* appear to correlate with the major steroids secreted *in vitro*. Many of these assumptions do not apply to a large number of *in vitro* studies done with radioactive *steroids* (progesterone or pregnenolone) used as precursors for studies of steroidogenesis in endocrine tissues.[11] The reasons for these differences are not apparent at this time. Studies of the latter type yield valuable information to the biochemist interested in pathways of steroid synthesis but often fail to provide a satisfactory means of correlation for puzzling clinical disorders.

PRINCIPLES

A rational discussion of gonadal endocrinology depends on recognition of certain basic principles.

1. The gonads are composed of different types of cells which, when grouped together, form morphologically distinct compartments.
2. Each compartment elaborates its own specific steroidal product.
3. The steroidal product of each compartment consists of more than a single steroidal hormone.
4. Each compartment is controlled by trophic substances of pituitary or placental origin.
5. When each compartment is stimulated by an appropriate trophic substance, it elaborates the entire steroidal product that it is capable of producing. The trophic hormone does not selectively cause a single steroid hormone to be produced by a given compartment.
6. A steroidal hormone secreted by a gonadal compartment may act at a distant site, may be converted peripherally to another metabolically active steroidal hormone, or may act *locally* in the gonad itself.

THE FOLLICLE

Evidence that the Graafian follicle is the major source of ovarian estrogen production is at best indirect. In the human, the proliferative phase of the menstrual cycle is associated with increased excretion of urinary estrogens, paralleling the growth of the follicle. Ryan and Smith[11] offered evidence that the human Graafian follicle is a source (though not necessarily the only source) of estrogen production; their results are shown graphically in Figure 2. The two estrogens, estradiol-17β (the most potent naturally occurring estrogen) and estrone, are the major radioactive steroids produced from acetate-1-^{14}C by the human follicle. Two androgens, Δ^4-androstene-3,17-dione and dehydroepi-

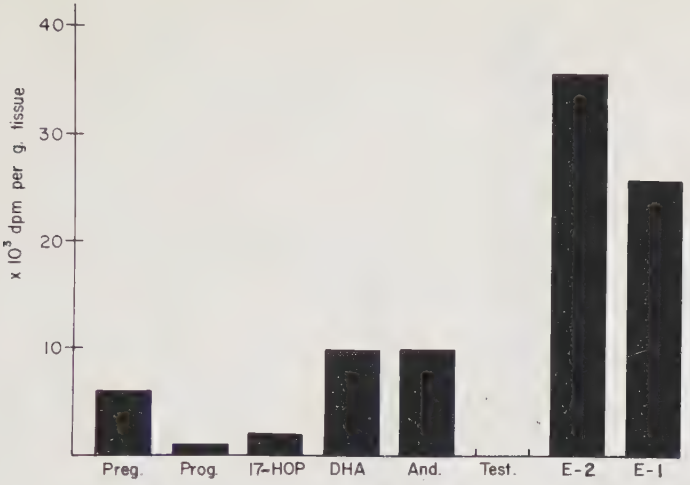

Figure 2. Profile of radioactive steroids formed *in vitro* from acetate-1-^{14}C by human ovarian follicular cyst lining (25 gm., 200 μc. acetate-1-^{14}C) Abbreviations: Preg. = 3β-hydroxy-Δ^5-pregnen-20-one. Prog. = progesterone. 17-HOP = 17-hydroxy-Δ^4-pregnene-3,20-dione. DHA = 3β-hydroxy-Δ^5-androsten-17-one. And = Δ^4-androstene-3,17-dione. Test. = testosterone. E-2 = estradiol-17β. E-1 = estrone. (Data from Ryan and Smith.[11])

androsterone, were found, but the potent androgen, testosterone, was not identified. Progesterone, considered an important intermediate for steroid synthesis, was found in distinctively low amounts. Although the tissues used by these investigators were obtained from patients given large amounts of exogenous gonadotropin, there is little reason to doubt that these experiments are representative of normal follicular tissue.

THE CORPUS LUTEUM

The human corpus luteum is distinctive among the species studied, since it appears to form androgenic and estrogenic steroids as well as progestins.[8, 12] Progesterone is the major steroid formed. An androgen, Δ^4-androstene-3,17-dione, and two estrogens, estradiol-17β and estrone, are formed from acetate-1-^{14}C. Significantly, testosterone is not found as a radioactive product after luteal slices have been incubated with acetate-1-^{14}C. The "profile" of steroids formed from acetate-1-^{14}C by the human corpus luteum (Fig. 3) is distinctive and characteristic, and differs significantly from that found with human follicular tissue (Fig. 2). Many human corpora lutea at various stages of the reproductive cycle have been studied with similar results. The absolute level of incorporation has been found to vary among individual corpora lutea and is probably a reflection of the gonadotropin environment from which the tissue was removed.[12] Nonetheless, the "relative" relationship among the steroids has been remarkably constant, progesterone being the major steroid produced under all experimental conditions. Among the gonadotropins tested, only substances with luteinizing hormone activity (human pituitary LH or human chorionic gonatropin)

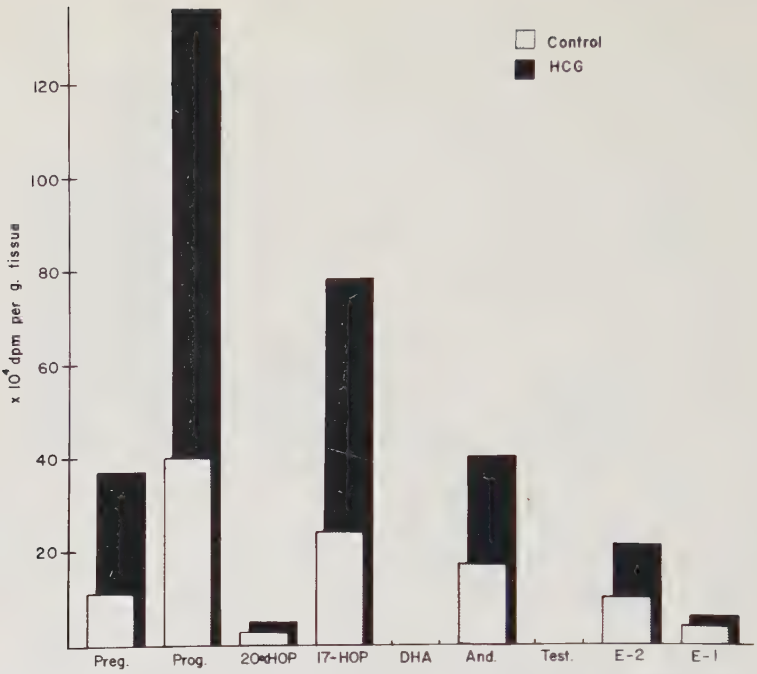

Figure 3. Profile of radioactive steroids formed *in vitro* from acetate-1-^{14}C (50 μc, 2.5 μ moles) by human corpus luteum. Effect of human chorionic gonadotropin (HCG) *in vitro* shown by darkened bars. Quantitative values obtained by reverse isotope dilution analysis. Abbreviations as in Figure 2; 20α HOP = 20α-hydroxy-Δ^4-pregnen-3-one.

were found to stimulate progesterone synthesis. Prolactin (lactogenic hormone, luteotrophic hormone or LTH) was inactive; this result suggests that, for the human at least, luteinizing hormone is "luteotrophic."[12]

THE OVARIAN STROMA

The biochemistry of the nongerminal elements has not been studied as extensively as that of the corpus luteum. Great variation in the histologic appearance of this tissue from fetal life to adulthood within a species, the wide variations in its appearance from species to species, and the lack of a discrete structure such as the corpus luteum has led to uncertainty regarding the biologic significance of this portion of the ovary.[2, 3, 12] Until recently, the evidence that the nongerminal elements of the ovary constitute a gland of internal secretion has been indirect and somewhat controversial.

A descriptive term for this compartment of the ovary presents some difficulties. In some species the nongerminal elements of the ovary have been referred to as the "interstitial" or "thecal" gland. In other species in which the adult ovary lacks typical epithelioid cells (the human), existence of such a specialized compartment has been denied.

In certain morbid states associated with "unusual" manifestations, these cellular elements *sometimes* assume the characteristics of the more typical "interstitial" or "thecal" cell.[3, 5, 6, 10, 12, 13] In this discussion, this portion of the human ovary will be referred to as the "stromal" compartment because of its accepted usage in human pathology.

Nature of the Steroids

Figure 4 shows the profile of radioactive steroids formed *in vitro* from acetate-1-^{14}C by human ovarian stromal tissue from a patient with an ectopic pregnancy.[10] Similar results have been obtained with normal stromal tissues obtained from patients who were not pregnant at the time of operation.

The steroidal profile is distinctive in that the major group of radioactive steroids is composed of the androgens: Δ^4-androstene-3,17-dione, testosterone, and dehydroepiandrosterone. Δ^4-Androstene-3,17-dione was always the major steroid formed by this tissue from radioactive acetate[9, 10, 12] Among the three different compartments studied, the ovarian stroma was the only one found to produce testosterone from radioactive acetate.[9] The estrogens, estradiol-17β and estrone, are formed in small but measurable amounts. Progesterone, the major steroid of the human corpus luteum, is formed only in trace amounts.

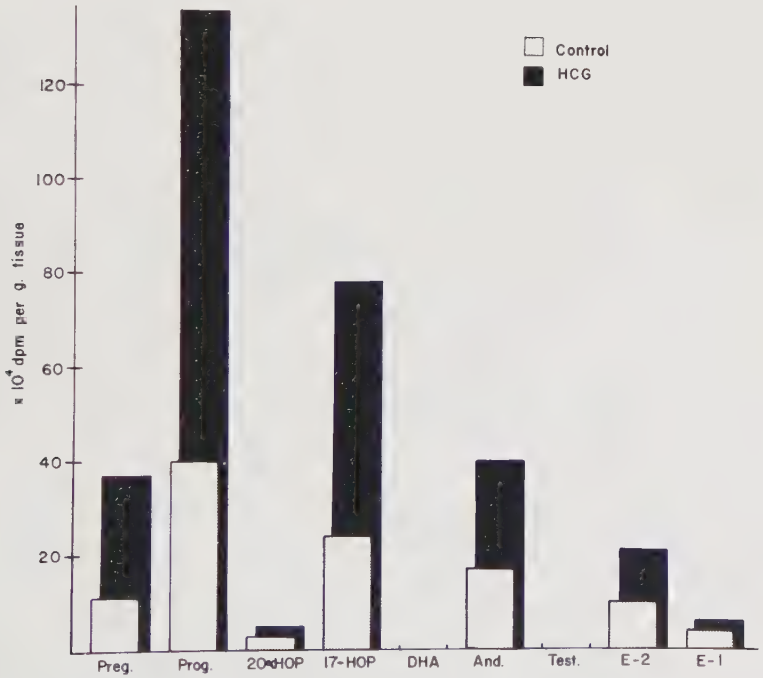

Figure 4. Profile of radioactive steroids formed *in vitro* from acetate-1-^{14}C (50 μc., 2.5 μ moles) by human ovarian stromal tissue from a patient with an ectopic pregnancy. Effect of human chorionic gonadotropin (HCG) *in vitro* shown by darkened bars. Quantitative values obtained by reverse isotope dilution analysis. Abbreviations as in Figure 2.

This steroidal pattern, with androgens as the major product, appears to be unique when compared with the patterns of radioactive steroids formed by the other two compartments of the human ovary. The accumulated evidence suggests that the nongerminal elements of the ovary form a distinct gland of internal secretion.[10] Additional studies suggest that the stromal compartment is under the control of trophic substances from the pituitary and placenta. It should not be unexpected that certain "unusual" manifestations of ovarian disease might originate in the pituitary and hypothalamus or placenta if we accept the existence of a stromal compartment that is under trophic hormone control.

CORRELATION

Certain clinical problems may be correlated with the material previously cited.

FOLLICLE. The well known granulosa cell tumor associated with pseudoprecocious puberty in the young girl probably best typifies neoplastic disorders of the follicular compartment.[4] Occurrence of non-neoplastic disorders of steroidogenesis in the follicular compartment is less well documented. Disorders of steroid production associated with luteinization of atretic follicles seem to resemble disorders of the stromal compartment and will be discussed in that section.

CORPUS LUTEUM. Disorders of the corpus luteum are unusual unless one wishes to include such ill-defined entities as the "persistent corpus luteum" or the "inadequate luteal phase" disorders. The former could, of course, be due to prolonged secretion of luteinizing hormone which is "luteotrophic" for the human corpus luteum.[8, 12] The luteal phase defect, conversely, could be due to inadequate secretion of luteinizing hormone from the anterior pituitary. The "luteoma of pregnancy," thought by some to be a neoplastic disorder of the corpus luteum, has been studied histologically and biochemically.[6, 12] The major steroid produced by a typical luteoma of pregnancy was found to be Δ^4-androstene-3,17-dione, the major steroid of the ovarian stroma.[6] No progesterone was found. The available evidence would indicate that this "unusual" disorder of the ovary is a result of intense stimulation of the stromal or thecal elements by the pregnancy gonadotropin. Virilization is unusual in mother or fetus but has been described. Most likely, protection from high circulating levels of androgenic steroids is afforded by rapid clearance and aromatization of C-19 steroids by the placenta. The "luteoma of pregnancy" is almost certainly not a disorder of the corpus luteum. If one insists that a functional "luteoma" be associated with excessive production of progestins, then a true functional luteoma (in the human) has still to be described.

THE OVARIAN STROMA. The compartment, which comprises most of the ovarian mass gives rise to most disorders commonly encountered in clinical practice. The polycystic ovary is probably the best example of a non-neoplastic disorder of this compartment. The steroidal profile of the polycystic ovary is identical to that of the normal stroma (Fig. 5). The

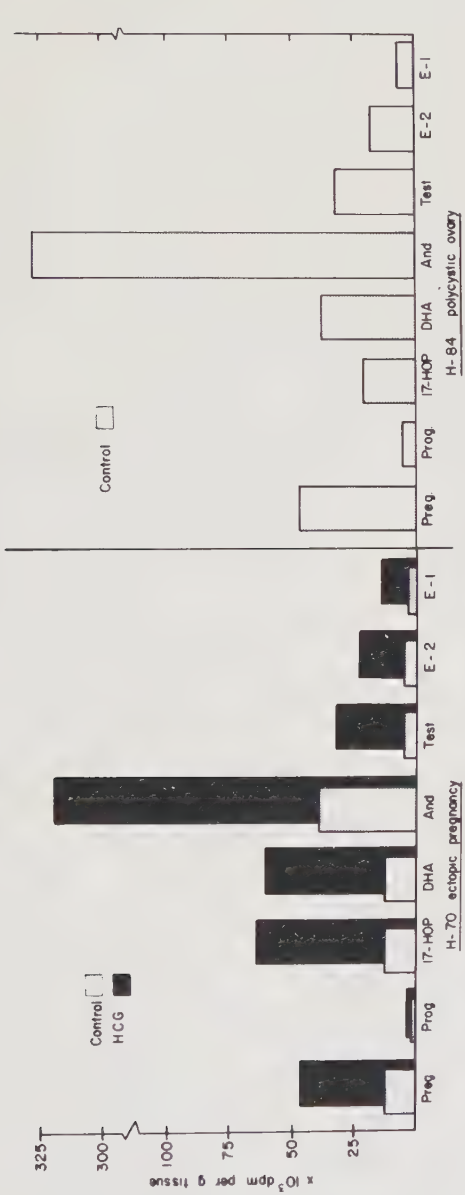

Figure 5. Profile of radioactive steroids formed *in vitro* from acetate-1-^{14}C (50 μc., 2.5 μ moles) by polycystic ovarian tissue (right) compared to the ovarian stroma from a patient with an ectopic pregnancy (left). Effect of human chorionic gonadotropin (HCG) shown by darkened bars (H-70, ectopic pregnancy); no gonadotropin effect shown for polycystic tissue (H-84). Abbreviations as in Figure 2.

available evidence would indicate that the polycystic ovary is a result of inappropriate high gonadotropin secretion, and that there is no biochemical defect in the ovary as the cause of the androgens produced in this disorder.[10] Other clinical disorders of "luteinization" appear to be similar to the polycystic ovary syndrome varying only in the degree of histologic change found in the stroma.[1, 3, 10, 12, 13] Postmenopausal stromal hyperplasia of the ovary would appear to represent another disorder of the ovarian stroma occurring in an older age group.[10] The clinical manifestations are variable but may include mild virilization and repeated uterine bleeding from a hyperplastic or atrophic endometrium.

The stromal compartment is probably the most common source of functional ovarian neoplasms. An accurate classification is difficult because of the histologic similarities among the neoplasms encountered.[5] Unquestionably a functional classification would be ideal. The usefulness of a functional approach in studying the "luteoma of pregnancy" has been referred to previously. Caution should be exercised in attempting to equate function of an ovarian neoplasm with histologic appearance.[5] Sensitive and specific methods for measurements of steroids in plasma (Δ^4-androstene-3,17-dione and testosterone) and urine (epitestosterone and testosterone) as well as gonadotropin measurements are needed for accurate preoperative study of patients with functional stromal neoplasms, but such techniques are not widely available. Considerable attention has been given to histologic study of functional ovarian neoplasms in the past.[5] It is hoped that more dynamic studies of the relationship of steroid production and gonadotropin levels in plasma and urine will lead to clarification of this confusing area. Certain primary or metastatic neoplasms in the ovary have been reported as producing disorders of steroid metabolism. At this time it is uncertain whether the steroids are produced by the tumor itself or by the surrounding stromal tissue. The *separated* elements have not been carefully studied, and the cellular source of the steroids produced in these conditions is still unknown.

SUMMARY

The steroidogenic capacities of three reasonably well defined ovarian compartments, the follicle, the corpus luteum, and the ovarian stroma, have been briefly described. Morbid states generally considered to be associated with "unusual" manifestations are commonly caused by deranged function of the stromal compartment. This ovarian compartment produces androgens as its major steroidal produce and appears to be under trophic hormonal control. Non-neoplastic "luteinizing" disorders of the stroma are possibly due to excessive stimulation by gonadotrophic substances originating from the pituitary (polycystic ovary syndrome) or the placenta (the luteoma of pregnancy). Functional neoplasms of the ovary are difficult to classify by histologic criteria alone. A functional classification of ovarian neoplasms based on their steroidogenic capacity would appear to offer much more information in regard to explaining "unusual" manifestations of ovarian disease.

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Unusual Manifestations of Graves's Disease

WILLIAM LOCKE, M.D.*

For the clinician, unusual manifestations of disease have the attraction of novelty. Knowledge of them also has importance, sometimes, in preventing the clinician from discarding a correct diagnosis or searching for a second diagnosis when one will do.

Some unusual manifestations of Graves's disease are unusual manifestations of hyperthyroidism. Others are derived from, or are associated in some usually inexplicable way with, the nonthyroidal component of Graves's disease. Among the former is hypercalcemia; among the latter, ophthalmoplegia. Some patients with Graves's disease are considered unusual because of the unusual course or severity of their disease, or because they lack one or more of the commonly conceived "essential" features of the syndrome. Some manifestations of Graves's disease are common, but not widely known.

USUAL MANIFESTATIONS

The representative patient with Graves's disease is an attractive, but irritable, jumpy young woman, who complains of nervousness, fatigue, and palpitation, gradually worsening during a period of several months, and who has widened palpebral fissures; hot, smooth, sweating skin; a pulse rate of more than 100 beats per minute; a tremor; and a small, firm, diffuse goiter. Other common, well recognized manifestations are intolerance of heat, loss of weight, shortness of breath, excessive hunger, ocular discomfort, tearing, frequent bowel movements without abdominal cramps, proptosis, a large pulse pressure, audible femoral pulses on auscultation, thyroidal bruits, weakness of the iliopsoas muscles, fast deep tendon reflexes, and, among the old, intermittent or persistent auricular fibrillation. Typically, laboratory tests give evidence of abnormally high levels of thyroid hormone in the body, avidity of thyroid gland for iodine, and refractoriness of the thyroid gland to normal stimulation and inhibition.

From the Department of Internal Medicine, Ochsner Clinic, New Orleans, Louisiana

UNUSUAL MANIFESTATIONS

AGE AND SEX. Graves's disease is commonest in the third and fourth decades of life, but patients of any age may acquire it, *a few congenitally*. In patients with congenital Graves's disease, with rare exceptions, the mother also has or has had the disease.[21] Less than 25 per cent of all patients with Graves's disease are male patients.

CLINICAL COURSE. Congenital Graves's disease is self-limited, lasting only a few weeks.[21] Postnatal Graves's disease may follow a variety of unusual courses. Some patients have *no symptoms*, and perhaps only a solitary sign, such as a goiter. Others recognize that they have been ill, but only after recovery. Some become prostrate in a few weeks. Among others, the disease is mild, waxing and waning for many years. Sattler[30] believed that eventual spontaneous cure may be expected in about one-fourth of patients with "mild" disease.

THE THYROID GLAND. A small number of patients *have no palpable goiters*; in 100 of my patients (Table 1), there were three such cases. This incidence corresponds well with Werner's[37] estimate, based on scintography, that between 1 and 3 per cent of patients have glands of normal size. These figures are not necessarily representative of all

Table 1. *Some Unusual Symptoms and Signs Among 100 Randomly Selected Patients with Graves's Disease* (69 Females, 31 Males)

CLINICAL MANIFESTATION	NO. CASES
Weight loss < 5 lb.	13
Weight gain	2
Onycholysis	13
"Bursitis"*	10
Poor appetite	9
Gynecomastia	6
Pulse rate < 80/min.†	6
Ophthalmoplegia	4
Thyroid felt normal	3
No thyrotoxic symptoms	3
Edema‡	3
Hyperpigmentation	2
Splenomegaly	2
Psychosis	2
Excessive thirst	2
Vomiting‡	1
Constipation	1
Vitiligo‡	1
Muscle tenderness	1
"Thyrotoxic myopathy"‡	1
Pretibial myxedema	1
Lid retraction, euthyroid	1
Severe rarefaction of bone§	1

*The term is meant to include bursitis, peritendinitis, pericapsulitis, etc.

†Patient partially treated in 2 cases.

‡Presenting complaint.

§The patient was a man, aged 65. Bone lesions were demonstrated first 5 months after a therapeutic dose of ^{131}I. Serum calcium and phosphorus were normal; serum alkaline phosphatase, above normal. No cause for the rarefaction of his bones other than Graves's disease was found.

groups of patients, however. Examiners differ greatly in their ability to detect thyroid enlargement, and the ease with which patients' thyroids can be felt varies widely. Even the most skillful examiner may be unable to detect a low-lying goiter in a fat, short, heavily muscled neck.

Nodules are incidental lesions in thyroid glands of Graves's disease. Beahrs and associates[4] found carcinomas in 0.5 per cent of 3,029 surgically removed glands. A lumpy thyroid is characteristic of patients with postoperative recurrent hyperthyroidism of Graves's disease.

THE PITUITARY GLAND. Detailed investigation of the pituitary gland of patients having Graves's disease is rare. Jailer and Holub[20] reported *enlargement of the sella turcica* in one patient. Hyperthyroidism disappeared after irradiation of the pituitary.

THE BREASTS. In 1840, Von Basedow[2] mentioned *gynecomastia* as a manifestation of what is here called Graves's disease, but remarkably little attention has been paid to it since then. Yet, it is relatively common. Berson and Schreiber[5] observed four patients with gynecomastia among 45 cases of hyperthyroidism, seen during a period of one and one-half years. It is not clear how many of the 45 patients had Graves's disease and how many were males. Thirty-one of my 100 patients were men, six of whom had gynecomastia. In one of my patients, not included in this series, *mastalgia* and gynecomastia were the chief complaints.

BODY WEIGHT. Eight of 80 female and 20 male patients with Graves's disease observed by Trotter and Eden[34] *gained weight* during the untreated phase of the illness. All eight were women between 15 and 28 years of age. One gained 4 pounds during the month before diagnosis; another, 44 pounds during the seven months before diagnosis. Thirteen of the 100 patients in my series lost less than 5 pounds. Two patients gained weight; one, a 17-year-old girl, gained 32 pounds.

SKIN AND APPENDAGES. Excessive separation of the nails from the nail beds (onycholysis) (Fig. 1) is another neglected but relatively common sign of Graves's disease. Onycholysis was present in 13 per cent of the 100 patients in my series. It forms part of other syndromes,[23] but in my experience it is rare among patients who do not have Graves's disease.

Vitiligo was the presenting complaint in one of the 100 patients in my series. Morgans[27] discovered it in 6 per cent of hers. Hyperpigmentation was noted in two of the patients in my series. This sign is due to the presence of excessive melanin and resembles the hyperpigmentation of Addison's disease to some degree, but tends to be spottier and less intense, though this is not always the case.

Pretibial myxedema (Fig. 2) is pathognomonic of Graves's disease. Usually it develops after treatment for thyrotoxicosis, as it did in the one patient in my series. The affected skin is thick, coarse, and nonpitting, and is said to resemble orange peel. The legs may become badly deformed, but fortunately the patient has little or no discomfort. The incidence of pretibial myxedema, when diligently sought, is about 50 per cent.[14]

Riddick[29] stated that *some patients think their skin is growing coarser*, even though to the examiner it has the fine, silky texture

FIGURE 1. Onycholysis of Graves's disease.

Figure 2. Pretibial myxedema. The patient also had severe exophthalmos.

typical of Graves's disease. The reason for this anomaly has not been thoroughly investigated.

THE EYES. Graves's disease spares the eyes in about one-third of patients. *Typical or atypical ocular abnormalities of Graves's disease* affecting one or both eyes *may occur in the absence of goiter, hyperthyroidism, or both.* The patient shown in Figure 3, who was untreated, had bilateral exophthalmos and retraction of the upper eyelids. The thyroid was firm and moderately enlarged. She was euthyroid, although thyroidal function was deranged, as revealed by failure of tri-iodothyronine to inhibit uptake of radioactive iodine. *Ophthalmoplegia* leading to *diplopia* was demonstrated in four of my 100 patients. The superior rectus muscles are often the first and most severely affected of the extra-ocular muscles. There is rough correlation between the degree of exophthalmos and the degree of ophthalmoplegia in many patients, but this observation is by no means invariable. Indeed, in one patient with severe ophthalmoplegia in my series, exophthalmometric readings were only 16 mm. in each eye.

An even rarer ocular manifestation of Graves's disease is a syndrome, sometimes called *optic neuropathy*, characterized by central and paracentral scotomas. In the 16 cases reviewed by Henderson,[18] the severity of the syndrome bore no relation to thyroid hormone levels, or to other ocular signs of Graves's disease. There were all degrees of visual loss, short of helpless blindness. Only one patient had pallor of the optic disks. Usually, vision was gradually lost during a period of a few weeks, and then regained, in whole or part. The old were affected oftener than the young; the average age of patients in Henderson's series was 56 years.

Of the same order of incidence as optic neuropathy are *glaucoma* and *papilledema*.[35] These two abnormalities seem to be closely related to the degree of exophthalmos, differing in this respect from ophalmoplegia and optic neuropathy. In far advanced exophthalmos *corneal swelling and ulceration* as well as *retinal hemorrhages, edema, exudates, and detachments* have been observed.[35]

CONNECTIVE TISSUE AND BONE. *Bursitis* or one of its relatives

Figure 3. An untreated euthyroid patient with retraction of the upper eyelids and exophthalmos (pulse, 76 beats/minute; BMR, −10; PBI, 6.5 mcg./100 ml.; kinemometer reading, 260 millisecs; ^{131}I uptake, 32 per cent. Treatment with 25 mcg. of tri-iodothyronine every eight hours for one week did not reduce the thyroidal uptake of radioactive iodine.

Figure 4. Clubbing of the fingers. The patient also had severe exophthalmos and pretibial myxedema.

(peritendinitis, pericapsulitis) was present in 10 per cent of patients in my series. The usual site was the shoulder, but one patient had trochanteric bursitis. Chapman and Maloof[9] reported coexistence of "subacromial bursitis" in 4 per cent of their patients, and Skillern[31] reported "periarthritis" of the shoulder in 6.7 per cent of his. He observed that the diagnosis of peri-arthritis of the shoulder is made in only 1.7 per cent of patients with nontoxic, nodular goiters.

Thyroid *acropachy* is a term applied to clubbing of the fingers (Fig. 4) and toes, formation of periosteal new bone involving the phalanges and other distal long bones, and swelling of the soft tissues of the arms and legs. It forms a triad with exophthalmos and pretibial myxedema. Most patients with acropachy are elderly. Gimlette[13] estimated that acropachy eventually develops in about 1 per cent of patients with "hyperthyroidism."

Rarefaction of bone (a characteristic difficult to measure) has been reported to occur in from 10 to 50 per cent of patients.[10] Radiologic examination may show that all of the skeleton is visibly demineralized.[8] This observation, together with the associated biochemical abnormalities to be considered later, suggests that the process should be classified as osteomalacia rather than osteoporosis.[8]

NEUROMUSCULAR SYSTEM. *Psychic disturbance* of varying degree is one of the commonest symptoms of hyperthyroidism. Sometimes it is extreme. Two of my 100 patients were psychotic. Boxall and associates[8] reported the case of a patient with Graves's disease whose psychosis came and went as his hyperthyroidism came and went. They thought that the patient "probably had an unstable psychiatric background."

Another common symptom of Graves's disease with hyperthyroidism (sometimes mistakenly labeled "arthritis" by the patient) is a mild degree of muscular weakness, particularly in the proximal muscles of the lower limbs. In *chronic thyrotoxic myopathy* (Fig. 5) muscular weakness and wasting, usually most noticeable in the muscles of the pelvic and shoulder girdles, but not confined to them, dominates the clinical picture. In rare instances, death due to respiratory failure has been attributed to thyrotoxic myopathy.[32] The myopathy vanishes when the associated (and presumably causative) hyperthyroidism is cured.[17, 26, 32] To my knowledge the pathologic process in Graves' disease, which affects the extra-ocular muscles to cause ophthalmoplegia and which may persist after the hyperthyrodism is cured, affects no other muscles. One patient in the present group of 100 was thought to exhibit thyrotoxic myopathy. About 40 cases had been reported before 1962.[17] Most patients have been middle-aged or elderly men.[19]

Apathetic hyperthyroidism[11, 25] most often affects middle-aged or elderly women. It is manifested clinically by "lethargy, placid facies, depressed mood, and 'mental and physical inertia.'"[25] The ocular signs of Graves's disease are said to be slight or absent. There are few signs of circulatory disease and little thyroid enlargement. Loss of weight is greater than in most patients with Graves's disease. The patient may gently slip into a stupor, become comatose, and die.[11] Obviously, the degree of "apathy" exhibited by patients with Graves's disease cannot be readily measured. Hence, the incidence of apathetic hyperthyroidism cannot be accurately estimated. In its fully developed form, it is either

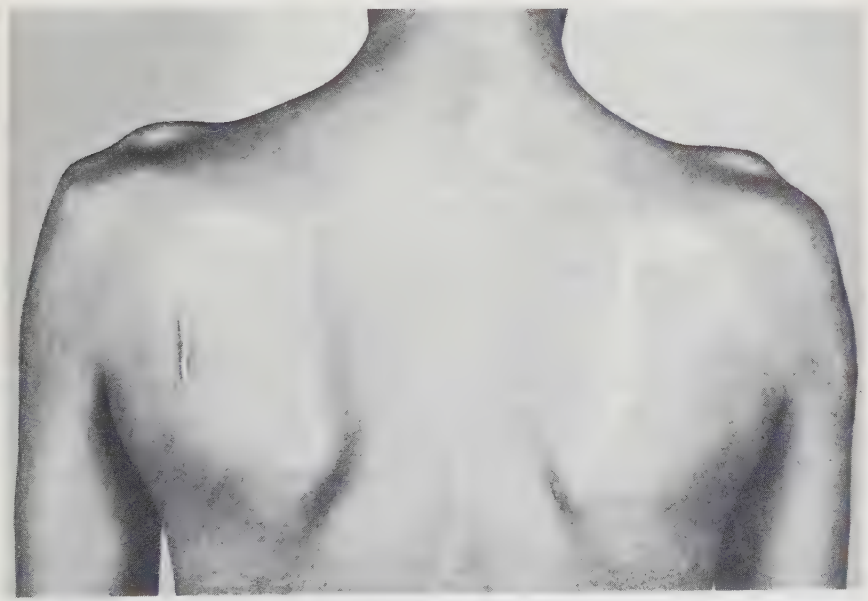

Figure 5. During a period of three years this 44-year-old man became so weak that eventually he had trouble swallowing. Though he had many signs of thyrotoxicosis, he had few or one of the usual symptoms of Graves' disease. Treatment with antithyroid drugs restored his strength and muscle mass in a few months.

very rare or infrequently recognized. This condition was not diagnosed in any of my 100 patients.

Both *periodic paralysis* and *myasthenia gravis* are associated with hyperthyroidism more often than chance can explain. In patients with periodic paralysis a familial history of the disease may be absent,[1, 28] although there may be a genetic basis for the association, since the incidence among Japanese seems to be much higher than among people of European descent. Okinaka[28] reported 119 cases among 6,333 patients operated on for hyperthyroidism in Japan, an incidence of 1.9 per cent. In uncomplicated periodic paralysis, males outnumber females 3 to 1; in Okinaka's series the incidence among males was 20 times that among females. Attacks of paralysis commonly cease when the hyperthyroidism is cured.

Approximately 5 per cent of patients with myasthenia gravis contract hyperthyroidism at some time during their lives,[26] but only a fraction of 1 per cent of patients with hyperthyroidism ever has myasthenia gravis. The exact incidence of myasthenia gravis is difficult to determine because of the similarity between the myasthenia of myasthenia gravis and that of hyperthyroidism. Years ago Waldenström[36] described a group of patients under the heading "*acute thyrotoxic encephalopathy.*" Some suffered from an *acute bulbar syndrome* characterized by paralysis of the pharyngeal muscles, palate, and vocal cords. Others experienced such symptoms as choreiform movements, aphasia, apraxia, confusional states, and a "true organic psychosis." Logathetis[22] referred to two patients in whom hyperthyroidism and a *bilateral pyramidal tract syndrome* with muscle wasting developed concurrently. The neuromuscular syndrome disappeared after the patients were relieved of hyperthyroidism.

THE CIRCULATORY SYSTEM. Six of my 100 patients, two of them partially treated, had *pulse rates of less than 80 beats per minute.* The lowest recorded figure in the untreated was 72 beats per minute.

Edema without recognized congestive heart failure or other usual cause of edema was the presenting symptom in three of my patients and in several reported cases.[12] It responds readily and favorably to treatment of the hyperthyroidism.

THE ABDOMEN. Tachdjian[33] stated that most patients with hyperthyroidism have *deranged hepatic function.* The derangement is usually slight, but in a few patients it is severe enough to cause jaundice. Often, it is the consequence of congestive heart failure. Rarely, there is acute diffuse hepatic necrosis. Greenberger[15] recently reported four cases of jaundice in which, he suggested, hyperthyroidism, while it lasted, unmasked a congenital defect in the metabolism of bilirubin.

Nine of my 100 patients had poor appetites. In one of my patients *vomiting* was the presenting complaint. Another patient, a physician, was surprised that he became *constipated.* One of my patients had been subjected to a useless laparotomy; others,[9, 24] have been similarly treated.

Splenomegaly was found in two of my 100 patients. Williams[38] placed the incidence of splenomegaly at 10 per cent.

THYROTOXIC CRISIS. When thyrotoxicosis suddenly becomes so severe that death is imminent, the patient is said to be experiencing

a *thyrotoxic crisis or storm.* McArthur and associates[24] commented, ". . . thyroid crisis is a syndrome of many facets and not a specific entity." Delirium, pulse rate of about 200 beats a minute, hyperpyrexia, and extreme weakness are common, but there is no uniformity in the clinical picture. Instead of being delirious, the patient may be apathetic. Vomiting, diarrhea, jaundice, abdominal pain, pulmonary edema, and oliguria have all occurred in patients experiencing thyroid crisis.

Like many endocrinologic crises, thyroid crisis usually develops in patients with severe endocrinologic disease who have been subjected to some nonendocrinologic stress, such as a surgical procedure. Fortunately, recent improvement in medical diagnosis and treatment have rendered thyroid crisis one of the rarest of the unusual manifestations of Graves's disease.

SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE. A few cases of *co-existent hyperthyroidism and hyperparathyroidism* have been reported.[7] Far more common is *hypercalcemia without recognized hyperparathyroidism.* Clerkin and associates[10] found hypercalcemia in six of 15 patients with hyperthyroidism; eight of the 15 were hyperphosphatemic. In 14 the serum alkaline phosphatase level was abnormally high, but four of these had bromsulphalein retention. Clerkin and associates attributed the hypercalcemia to hyperthyroidism and suggested that in similar cases persistence of hypercalcemia after the patient has become euthyroid warrants search for other causes of hypercalcemia. Guyer[16] reported a case of *hypercalcemia, hypophosphatemia, and hypercalciuria* corrected by treatment of thyrotoxicosis.

In most instances, disturbance of calcium and phosphorus metabolism does not produce recognizable symptoms. In nine cases referred to by Bauman and co-workers,[3] however, hypercalcemia, later eliminated by controlling the hyperthyroidism, was blamed for anorexia, nausea, vomiting, and severe weakness. In one case, biopsy showed renal scarring and calcinosis.

TESTS OF THYROID FUNCTION. Of the many thyroid function tests described through the years, the usual ones performed today are measurements of serum protein-bound iodine concentration, the 24-hour thyroidal uptake of radioactive iodine, basal metabolic rate, and the duration of the deep tendon reflexes. Recently, the "T_3" test was introduced. Each of these tests, when performed on patients with untreated Graves's disease, sometimes gives normal results. Blackburn and Power[6] found that among 147 such patients 4.7 per cent had normal protein-bound iodine concentrations, 12.2 per cent had normal basal metabolic rates, and 16.3 per cent had normal thyroidal radioactive iodine uptakes. Corresponding values with respect to measurements of the duration of deep tendon reflexes and results of the "T_3" test are difficult to estimate owing to conflicts in published reports. Doubtless, these will abate as more experience is gained.

The foregoing, being a summary in itself and little more than a list of unusual manifestations of Graves's disease, is scarcely susceptible to further useful summarization. Perhaps, the conclusion reached by Chapman and Maloof[9] that Graves's disease impinges on most, if not all, medical specialties should be simply reemphasized.

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Unusual Antimicrobial Toxic Reactions

GEORGE A. PANKEY, M.D.

Antimicrobial agents are presently available for the treatment of infectious diseases caused by bacteria, fungi, Mycoplasma pneumoniae, rickettsia, protozoa, metazoa, Miyagawanella (lymphogranuloma venereum and psittacosis agents), and Chlamydozoon (trachoma and inclusion conjunctivitis agent). Though often lifesaving, these drugs have introduced some problems for the individual as well as for society in general. These include "new" diseases as a result of toxicity (staining of fetal teeth by tetracycline) and sensitization of persons who have never received a certain antimicrobial agent as therapy but have been unknowingly exposed (contamination of milk by penicillin when used to treat mastitis in cattle, etc.). The total population increase, as well as the increase in life expectancy in the United States, has been due largely to antimicrobial therapy, because of reduced infant and maternal mortality rates, and treatment of bacterial pneumonia in the elderly. Few persons alive today have escaped receiving an antimicrobial agent at some time. It is estimated that more than two billion dollars is spent on antimicrobials yearly in the United States, representing around 50 per cent of all prescriptions written. The physician has more than 35 different antimicrobials in more than 400 dosage forms from which to choose.

Minor and major toxic effects of some of the antimicrobial agents used *systemically* will be discussed, with special emphasis on the less common toxic reactions. The agents and the respective toxicities will be presented individually. It should be pointed out that little is known of the toxicity of combinations of two or more of these agents administered at the same time. Unfortunately, patients receiving these combinations are usually difficult to evaluate because of the nature of the primary disease and other medications the patient may be receiving at the same time. The antituberculous agents are probably the best studied combination, but there are surprisingly few data even for this group.

Certain persons are more prone to toxic manifestations as a result of

From the Section on Infectious Diseases, Department of Internal Medicine, Ochsner Clinic, New Orleans, Louisiana

antimicrobial therapy. They include the very young with immature enzyme (detoxifying) systems and those with hepatic or renal disease. Older persons may have considerable renal disease and still maintain a normal blood urea nitrogen level and, therefore, antimicrobials excreted by the kidneys may accumulate rapidly in these patients. Probably the biggest single obstacle to good antimicrobial management is the difficulty of determining the level of the antimicrobial agent in the body fluids. The sulfonamides are notable exceptions to this.

A careful history regarding allergy, especially to antimicrobials and other drugs, remains the best way to prevent hypersensitivity reactions in patients. Even with a negative history, an anaphylactic reaction may occur, especially after parenteral administration of an agent such as penicillin G. The physician administering antimicrobial agents parenterally in the home should remain with the patient for at least 30 minutes and have aqueous epinephrine, adrenocortical steroids for parenteral use, diphenhydramine, a vasopressor such as metaraminol, and a tracheal trocar in his bag. The same principles should be observed when antimicrobials are administered parenterally in the physician's office or hospital emergency room. The tragedy of a death due to anaphylaxis from antimicrobial therapy would be extremely rare if these simple precautions were uniformly observed. Fortunately, anaphylactic reactions after orally administered antimicrobials are far less common, although some believe that the same precautions should be observed for the penicillins administered in this fashion.

The antimicrobial agents will be considered according to the type of microorganisms against which they are principally active. Comments regarding dosage refer to adults only.

ANTIFUNGAL AGENTS

Amphotericin B

This fungistatic antibiotic is the most effective agent available for the treatment of *systemic* candidiasis, mucormycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, and aspergillosis. It is also the preferred treatment for North American blastomycosis. It is given intravenously and can cause chemical phlebitis, which usually responds satisfactorily to administration of 100 mg. of phenylbutazone, three times a day for five days, and application of heat. Addition of 20 to 40 mg. of heparin to the infusion plus use of a pediatric scalp vein needle helps prevent phlebitis due to this and most other antimicrobials administered intravenously.

Unfortunately, many toxic effects of amphotericin B occur in all patients treated with this agent. These include fever (up to 105° F.). true rigors, headaches, nausea, vomiting, anxiety, and abdominal pain during or immediately after completion of the usual daily six-hour infusion of 500 ml. of 5 per cent solution of dextrose in water with amphotericin B. These toxic effects are more common with the first ten treatments and may be lessened or prevented by intramuscular administration of 50

mg. of chlorpromazine and diphenhydramine, 30 minutes before beginning the infusion, and 100 mg. of hydrocortisone intravenously when the infusion is started. After the first ten treatments, tolerance to amphotericin B usually permits discontinuance of one or more of these drugs.

Later toxic effects include normocytic normochromic anemia, which is reversible, but is treated with blood transfusion while therapy is continued, if the hemoglobin is less than 10 gm./100 ml. Complete blood counts are performed weekly. In two patients treated recently, reversible granulocytopenia developed in the peripheral blood. Treatment was not altered, and no apparent ill effects have occurred.

The metabolic fate of amphotericin B is unknown, but only a small portion is excreted in an active form in the urine. Nephropathy with increased blood urea nitrogen and creatinine levels; decreased renal concentrating ability; decreased phenolsulfonphthalein excretion; decreased clearance of urea, creatinine, and inulin levels; and decreased clearance of para-aminohippurate occurs, and usually some irreversible renal damage results if a total of 2.5 gm. of amphotericin B is given.[1,2] The pH of the urine is frequently alkaline in addition to containing cellular elements and casts. Proteinuria is uncommon. Maintenance of acid pH urine with ascorbic acid has not prevented rise in blood urea nitrogen or creatinine levels. If daily administration of amphotericin B results in a rise in blood urea nitrogen or creatinine, the drug may be given on alternate days. The goal is to keep the blood urea nitrogen level less than 40 mg./100 ml. or the creatinine less than 2 mg./100 ml. One of these determinations should be obtained weekly, and if values exceed the levels quoted, treatment should be discontinued until acceptable levels are obtained.

Hypokalemia with increased urinary excretion of potassium usually occurs, and severe muscle weakness and paralysis have been reported. I routinely prescribe a solution of potassium salts in a dosage of 15 mEq. or more four times a day to maintain normal serum potassium concentration.

Idiosyncratic reactions, including anaphylactoid shock, thrombocytopenia, acute hepatic failure, flushing, vertigo, generalized pain, grand mal convulsions, cardiac arrest, peripheral neuropathy, and ventricular fibrillation, rarely occur. I obtain weekly serum for glutamic pyruvic transaminase determinations and have occasionally noted slight rises.

Griseofulvin

This fungistatic antibiotic is used in the treatment of cutaneous infections caused by microsporum, epidermophyton, and trichophyton (usually 0.5 to 1 gm. every day for six to 24 weeks). Griseofulvin is mainly fixed and carried with keratin in the body, the remainder being detoxified in the liver. Most patients tolerate it well.

An occasional patient will have an oral or gastrointestinal disturbance, such as dry, painful, or black tongue; angular stomatitis; anorexia; epigastric pain; nausea; vomiting or reactivation of chronic colitis with bloody diarrhea. *Rarely*, dermatologic lesions occur, in-

cluding urticaria (sometimes angioneurotic edema), petechiae, erythemas, lichen planus-like eruptions, pruritus, and photosensitivity (including a lupus erythematosus-like syndrome). Candidiasis of the skin and mucous membranes may occur during treatment with griseofulvin.

Rarely, neurologic reactions occur, including blurred vision, disorientation, nightmares, vertigo, and potentiation effects of alcoholic beverages. Lack of coordination and lapses of attention and memory were noted in two pilots during prolonged treatment with griseofulvin.[3] Headache during the first few days of treatment is rather common but subsides even though use of the drug is continued. Granulocytopenia that is reversible and probably of no clinical significance occasionally occurs.

Miscellaneous (and nonspecific) reactions include thirst, fatigue, generalized malaise, engorgement of the breast, and fainting. Griseofulvin affects porphyrin metabolism experimentally, and it has precipitated attacks in patients with acute intermittent porphyruria during remission. This fungistatic antibiotic has been reported to decrease the severity of pain in patients with angina pectoris and result in improvement in some patients with shoulder-hand syndromes. The chemical structure of griseofulvin is somewhat similar to colchicine and apparently potentiates its action in the treatment of acute gouty arthritis. Sodium variation antagonism may occur.

AGENTS PRINCIPALLY ACTIVE AGAINST GRAM-POSITIVE BACTERIA

Cephalothin

This bactericidal antibiotic is excreted mainly by the renal tubules, as is penicillin G; however, when given alone, it does not accumulate or produce toxicity in patients with poor renal function. This is presumably because of rapid inactivation by deacetylation in the liver.[4] It should be administered only parenterally, being extremely painful when given intramuscularly.

Cephalothin is effective against most bacteria which are penicillin-sensitive. Fortunately, cross-sensitivity between the penicillins and cephalothin does not occur; therefore, cephalothin can be administered safely to penicillin-allergic patients. Hypersensitive reactions to cephalothin, itself, can occur, the most common of which are eosinophilia alone or rashes. Other toxic manifestations are infrequent, but reversible neutropenia and elevation of the serum glutamic oxalacetic transaminase (SGOT) level may occur. Reversible renal failure has occurred in three patients with severe systemic disease who were receiving cephalothin (12 to 18 gm. daily intravenously) plus other drugs, including other antibiotics, such as colistimethate and rolitetracycline. Patient with renal dysfunction should probably not receive more than 6 gm. of cephalothin a day. On the other hand, a penicillin-G-allergic patient was given 18 gm. of cephalothin intravenously every day for 30 days for alpha hemolytic streptococcal bacterial endocarditis without

difficulty.[5] A positive reaction to the direct Coombs' test may occur in cephalothin-treated patients with azotemia.

Erythromycin

This bacteriostatic macrolide antibiotic is effective treatment for Mycoplasma pneumoniae infections and can be used as an alternative drug for the penicillins in the treatment of non-life-threatening infectious diseases. Since it is excreted primarily in the bile, the usual dose (250 to 500 mg. every six hours) does not need to be altered for patients with renal disease.

Erythromycin has caused no serious toxic effects. Minor toxic effects (primarily gastrointestinal) are common, however. These include stomatitis, black tongue, nausea, abdominal pain, vomiting, loose stools occasionally with proctitis, and alcoholic intolerance. These reactions rarely necessitate discontinuance of administration of erythromycin. Headaches, dizziness, rashes, and superinfection with Candida are uncommon. Discoloration of teeth and enamel hypoplasia due to erythromycin in one child have been reported.

I do not prescribe erythromycin estolate or the similar triacetyloleandomycin because they can produce hepatic disease, and they have no advantage over plain erythromycin.[6] Erythromycin for parenteral administration is available, but as a rule, if the patient is ill enough to require administration by this route, another antibiotic should be used, such as one of the penicillins, cephalothin, or vancomycin.

Lincomycin

This antibiotic is excreted primarily in the bile with up to 30 per cent in the urine. It has not been used extensively enough to evaluate its proper place in therapy of infections caused by gram-positive cocci, although it shows some promise in the treatment of staphylococcal osteomyelitis in the penicillin-allergic patient. When administered parenterally, it is well tolerated. Diarrhea, which is apparently the most frequent toxic effect of oral administration, has necessitated discontinuance of use of the drug on some occasions. With more extensive use of this antibiotic other toxic effects may become apparent.

Novobiocin

I do not prescribe this bacteriostatic antibiotic because of its high incidence of toxicity (jaundice, rashes, blood dyscrasias, fever, and other signs of hypersensitivity) and because of the availability of more effective and less toxic agents.[7, 8] Use of fixed combinations of antibiotics, such as tetracycline and novobiocin, is not recommended.

The Penicillins

Penicillin G (Benzyl Penicillin). This bactericidal agent is excreted by the renal tubules with some inactivation in the liver. With the exceptions of fever and hypersensitivity reactions (contact dermatitis, urticaria and delayed serum sickness, and immediate anaphylaxis),

toxic manifestations of penicillin G and alpha phenoxymethyl penicillin are unusual. Direct Coombs-positive hemolytic anemia rarely occurs.[9] Penicillin G has been implicated as an activator of systemic lupus erythematosus (SLE).[10] Acute psychotic reactions may develop after injections of aqueous procaine penicillin. Such reactions are probably due to intravascular leakage of procaine.

When large amounts of penicillin G are given, the potassium or sodium content may be significant, especially if renal failure is present (each million units contains approximately 1.7 mEq. of potassium *or* sodium plus 0.3 to 0.4 mEq. sodium in the sodium citrate buffer). Irritation of the central nervous system manifested by seizures occasionally develops in patients given large doses of penicillin G (20 to 80 million units daily), but usually such patients have underlying cerebral disease.[11] Intrathecal administration is contraindicated because of neural irritant properties. Nephritis (presumably hypersensitivity type) associated with penicillin G and methicillin therapy has been reported.[12] The urine contains cellular elements (especially red blood cells and red blood cell casts), and proteinemia may be striking.

The mechanism of development of hypersensitivity to the penicillin is poorly understood. In some patients this hypersensitivity apparently disappears spontaneously. We do not have any completely reliable laboratory or clinical tests to enable us to predict whether an anaphylactic reaction will follow penicillin therapy. There is no justification for administration of any of the penicillins (including penicillin O) to a patient known to be allergic to penicillin, because other antibiotics, such as cephalothin and vancomycin, are effective. When penicillin therapy is initiated parenterally, the precautions mentioned previously should be observed. If anaphylaxis occurs (hypotension, wheezing, angioneurotic edema), I administer aqueous epinephrine (1:1000, 0.5 to 1.0 ml.), methylprednisolone (40 to 125 mg.) or hydrocortisone (200 to 500 mg.), and diphenhydramine (50 mg.) in that order, all intravenously through the tubing of a 5 per cent dextrose infusion. Penicillinase is not used. Oxygen by mask is given and an open airway is maintained (with tracheostomy if necessary). Patients usually respond to such treatment rapidly, and further use of epinephrine is rarely required. If hypotension persists, vasopressors, such as metaraminol or levarterenol, are given. Administration of adrenocortical steroids and diphenhydramine is continued until the body has had time to excrete or inactivate the particular penicillin given. Benzathine penicillin remains in the body for at least three weeks, but prednisone in a dosage of 10 mg. every eight hours and diphenhydramine (25 mg. every six hours) usually prevent hypersensitivity symptoms after control of the initial episode of hypotension.

METHICILLIN. This antibiotic is used only to treat severely ill patients with infections caused by Staphylococcus aureus. It is administered intravenously (usually 6 to 12 gm. a day with physiologic saline solution) and can cause fever and hypersensitivity reactions similar to penicillin G. Rarely, reversible bone marrow depression (especially erythroid aplasia) has been noted. Associated with this depression is elevated serum iron concentration and saturated total iron-binding

capacity.[13] To my knowledge there have been no reports of aplastic anemia associated with methicillin therapy. On the rare occasion when clinical and laboratory signs of renal and hepatic disease have been noted during methicillin therapy, a direct cause and effect were not established.

Cloxacillin. This semisynthetic penicillin is active against penicillinase-producing Staphylococcus aureus strains and is well absorbed orally. It is preferable to the similar oxacillin, especially in children. Cloxacillin, oxacillin and nafcillin differ from the other penicillins in being excreted primarily in the bile. Anaphylactic reactions do not appear to occur as frequently to cloxacillin as to penicillin G or methicillin, possibly because no parenteral form is available, as well as the fact that it has been less extensively used. Cross-sensitivity between the various types of penicillins may or may not occur.

Rashes and fever occur, as well as minor gastrointestinal complaints, such as bitter eructations and nausea, the latter rarely necessitating discontinuance of administration. I have seen no patients with overt hepatic or renal disease associated with cloxacillin therapy. Slight elevations of SGOT have occurred during therapy.

Ampicillin. This bactericidal antibiotic is rapidly excreted in the urine and is effective against some gram-negative bacilli (E. coli, Shigella, Salmonella, Hemophilus, and Proteus mirabilis) as well as gram-positive cocci with exception of penicillinase-producing staphylococci.[14] Because of the greater variety of antimicrobial action, superinfections with Candida species would be expected to be more common than with the other penicillins.

Recently, I studied 45 consecutive patients treated with ampicillin. In three (6.7 per cent) a rash thought to be due to the drug developed, two early and one late in course of treatment. In two others clinical candidiasis developed and five complained of loose stools or diarrhea. Quantitative fecal cultures for Candida species on treatment days 1, 5, and 10, respectively, were performed on 32 patients given 500 mg. every six hours primarily for genitourinary infections. Approximately one-half showed a great increase in Candida species in the stool at the end of treatment with a similar number showing no change throughout treatment. There was no correlation between the loose stools or diarrhea and the number of colonies of Candida species in the stool.

It is my impression that rashes (possibly not all on a hypersensitivity basis) occur more frequently with ampicillin therapy than with the other penicillins. Rises in SGOT have been reported, but no clinical hepatic or renal disease has been attributed to ampicillin.

Nafcillin. I do not prescribe this agent because it has no advantage over the previously discussed penicillins and it is not absorbed from the gastrointestinal tract as well as cloxacillin.

Vancomycin

This bactericidal antibiotic is not absorbed when given orally, but may be administered in this fashion for treatment of staphylococcal pseudomembranous enterocolitis (0.5 gm. every six hours). It is given

intravenously for severe infectious disease due to penicillin G or methicillin-sensitive microorganisms in a penicillin- *and* cephalothin-allergic patient. Unfortunately, phlebitis with thrombosis occurs in most patients in spite of all precautions.

Vancomycin is excreted primarily by glomerular filtration, and very high serum levels can occur in patients with renal disease given ordinary doses (0.5 to 1.0 gm. every six hours). The most serious complication of vancomycin therapy has been decrease in hearing or total deafness, but this is rare in patients with normal renal function. Reversible nephropathy may occur but has not been a problem with recent lots of the drug. Drug fever, urticarial and macular rashes, and generalized tingling (during vancomycin infusion) may occur. Allergic reactions and peripheral neuropathy are rarely associated with this agent.

AGENTS PRINCIPALLY ACTIVE AGAINST GRAM-NEGATIVE BACILLI

Chloramphenicol

I use this antibiotic only in the rare tetracycline-allergic patient with rickettsial or Miyagawanella infection. Chloramphenicol is the leading cause of drug-induced aplastic anemia in the United States. In addition, it can produce acute and fatal circulatory collapse in patients deficient in hepatic-conjugating enzymes as well as cause serious visual disturbances (amblyopia, decreased visual acuity, and scotomata).[15] Agranulocytosis, thombocytopenia, and hemolytic anemia in glucose-6 phosphate dehydrogenase (G6PD) deficient persons may also occur.

Colistimethate and Polymyxin B

For practical purposes, these two bactericidal preparations may be considered identical. Both are administered parenterally for systemic infection caused by Pseudomonas, Klebsiella-Aerobacter group, and some other gram-negative bacilli. Colistimethate (polymyxin E) is preferred for intramuscular injection (usually 100 mg. every eight hours or 2.5 to 5 mg./kg. body weight/day) because it is combined with dibucaine and is less painful. Polymyxin B may be administered intramuscularly or intrathecally. The usual intravenous or intramuscular dose is 50 mg. every eight hours (1.5 to 2.5 mg./kg. body weight/day).

The most distressing toxic effects involve the nervous system. These include paresthesia (especially circumoral), nystagmus, ataxia, and dysarthria. Fortunately, these effects may be minimized or eliminated by a decrease in the dose, and apparently there is no permanent damage. Respiratory arrest (apnea) due to neuromuscular blockade during use of these agents has been reported.[16] This complication is not common and appears to be associated with high blood levels. The latter is most likely to occur in patients with renal disease, as the compounds are excreted by the kidneys. Increased susceptibility to this complication would be expected in anesthetized patients and those with

myasthenia gravis. It is not known whether neostigmine (Prostigmine) or calcium ion (calcium chloride or gluconate IV) is the better antidote.

Dermatitis, drug fever, and nephrotoxicity (rising blood urea nitrogen level with or without formed elements in the urine) all may occur, but nephrotoxicity has not been a problem if recommended doses are not exceeded. Obviously, in the presence of renal disease the dosage must be adjusted. If the creatinine is 1.5 to 5 mg./100 ml., an initial loading dose of 2.5 mg./kg. body weight of colistimethate (1 mg./kg. if polymyxin B is used) is given during the first 24 hours, and every two to three *days* afterward. If the creatinine level is higher than 5 mg./100 ml. after this initial dose, the same dosage is repeated every six or seven *days*.

Kanamycin

This bactericidal antibiotic is excreted by glomerular filtration and is administered intramuscularly or intravenously in the treatment of serious infectious diseases due to most gram-negative bacilli, including Klebsiella-Aerobacter group, paracolon, Proteus species, and E. coli. The average adult dose is 0.5 gm. every eight hours (10 to 15 mg./kg. body weight/day). Circumoral and other paresthesias, peripheral neuropathy, restlessness, blood dyscrasias, rashes, headaches, visual complaints, drug fever, and other allergic reactions occur rarely with kanamycin therapy.

Nephrotoxicity with azotemia occurs in patients with previous renal disease unless dosage is adjusted. Neuromuscular blockade (succinylcholine-like effect) with respiratory paralysis and apnea may follow intraperitoneal, intrapleural, or rapid intravenous administration, particularly if associated with ether anesthesia. Kanamycin administered by these routes is contraindicated in ether-anesthetized patients, patients with myasthenia gravis, and those known to be hypersensitive to succinylcholine. Experimental studies suggest that calcium chloride (0.5 to 1.0 gm. intravenously) is the preferred antidote.[17] Some believe neostigmine is contraindicated, since it may worsen the neuromuscular blockade.

The most frequent and, unfortunately, a serious toxic effect of kanamycin is damage to the cochlear division of the eighth cranial nerve. Permanent, bilateral, perceptive deafness may occur, but it is unusual in patients treated for no more than two weeks, unless renal disease is present. Daily questioning regarding tinnitus and pressure or fullness in the ears; biweekly creatinine or blood urea nitrogen determinations; and weekly audiography should be performed during kanamycin therapy, and use of the drug discontinued if the infection is controlled and any of these tests reveal abnormalities. Obviously, in a severely ill patient with, for example, Proteus vulgaris pneumonia and septicemia, deafness may have to be accepted as a price for survival. Other potentially ototoxic antibiotics, such as neomycin, streptomycin, vancomycin, and viomycin, should *not* be administered concurrently.

If patients with renal disease require kanamycin treatment, the following is recommended: (1) Creatinine value of 1.5 to 5 mg./100 ml.,

a single 1 gm. dose followed by 0.5 gm. every two to three *days*. (2) Creatinine value of more than 5 mg./100 ml., a single 1 gm. dose followed by a single 0.5 gm. dose in four *days*.

Nalidixic Acid

This synthetic antimicrobial agent is excreted primarily in the urine, and is used for the treatment of genitourinary infections. It has not been used extensively enough for adequate evaluation of toxic effects; however, a few interesting observations have been made.

Rashes, nausea, vomiting, eosinophilia, polyarthritis, and dizziness may occur. Overdosage (usually 0.5 to 1.0 gm. four times a day is given) may precipitate convulsions in patients with disease of the central nervous system and cause convulsion, hyperglycemia, and glycosuria suggesting diabetic ketosis. The plasma acetone value is normal in the latter.[18] Visual difficulty, including diplopia, and photosensitivity reactions may occur during therapy with nalidixic acid. The latter reaction probably will eventually be found to be associated with a lupus erythematosus-like syndrome.

An increase in the thymol turbidity reaction and SGOT has occurred. Patients receiving nalidixic acid should have periodic liver function tests and complete blood counts until more is known about the drug. Of practical interest is the fact that a glucoronide conjugate of nalidixic acid, which is excreted in the urine, may give a false-positive glucose reaction with Clinitest or Benedict's solution, but not with Clinistix. Because of the rapid emergence of nalidixic acid resistant bacteria during treatment, this agent will probably be used less frequently in the future.

Neomycin

This antibiotic is similar to kanamycin. It is not used systemically but a small amount may be absorbed from the gastrointestinal tract with oral use for hepatic disease, and if renal disease is also present, enough may accumulate to produce toxic effects similar to kanamycin. Neuromuscular blockade similar to kanamycin may occur if neomycin is used intraperitoneally.

Nitrofurantoin

This synthetic agent is widely used by urologists in the treatment of genitourinary infections and is probably the leading cause of nausea, vomiting, and drug fever in their patients. I do not prescribe this expensive agent, which "sterilizes" the urine but does not cure the infection. In addition to the toxic effects already mentioned, severe peripheral neuropathy,[19] allergic tracheobronchitis, anaphylaxis, rashes, and anemia (both hemolytic in G6PD-deficient individuals and megaloblastic) may occur.[20]

An unusual, but probably more common than generally realized toxic manifestation, is small pulmonary infiltrations with or without eosinophilia which clinically resemble pulmonary emboli. In one patient who had retropubic prostatectomy, fever developed during nitrofurantoin therapy and its administration was discontinued. Correlation

of the febrile episode with the drug, however, was not appreciated and administration of nitrofurantoin was restarted. Dyspnea, tachypnea, tachycardia, apprehension, fever, and substernal pain developed, and coarse breath sounds were heard. No abnormalities were detected in roentgenograms of the chest and electrocardiograms. Suppurative pelvic thrombophlebitis with pulmonary emboli was suspected, and the inferior vena cava was ligated. The patient improved, but administration of nitrofurantoin had also been stopped because of the operation. One week later, administration of nitrofurantoin was again started, and fever, thoracic pain, and coarse breath sounds returned. This time the patient had informed his physicians that the medication was making him sick.

Another patient taking nitrofurantoin showed signs and symptoms suggestive of pulmonary embolism. No abnormality was noted in roentgenograms of the chest, but the lung scan supported the diagnosis (Fig. 1). The patient rapidly improved when nitrofurantoin was with-

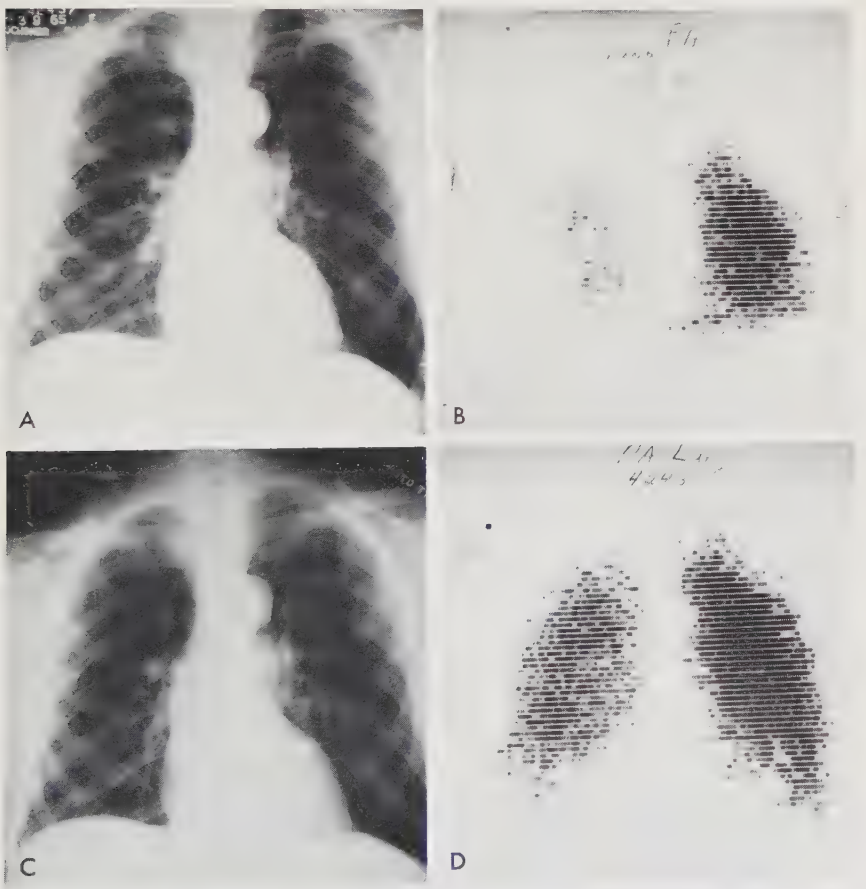

Figure 1. Nitrofurantoin toxicity, *A*, *B*, Postero-anterior roentgenogram and lung scan on March 9, 1966, the latter suggesting pulmonary embolus. *C*, *D*, Follow-up studies on March 15, 1966, after discontinuing nitrofurantoin. Note normal roentgenogram and rapid clearing.

drawn, and six days later, a lung scan showed considerably more clearing than would be expected if pulmonary embolism had occurred.

Chills and fever developed in a physician while receiving nitrofurantoin for prostatitis. Changes suggestive of pulmonary emboli were demonstrated in roentgenograms of the chest. Fortunately, eosinophilia of 24 per cent was demonstrated, and a diagnosis of nitrofurantoin toxicity was made. Symptoms subsided upon discontinuance of administration of the drug. These three cases are presented to focus attention on a toxic manifestation of nitrofurantoin that can resemble a life-threatening disease (pulmonary embolism) which, if present, would demand drastic therapeutic measures (possibly inferior vena cava ligation).

Streptomycin

This bactericidal antibiotic has been used extensively in the treatment of mycobacterial and Pasteurella infections, but always in combination with other antimicrobials, as otherwise bacterial resistance develops rapidly. Hypersensitivity reactions to streptomycin occasionally occur, including dermatitis, fever, eosinophilia, and rarely, angioneurotic edema.[21] Much less common complications include bone marrow depression, peripheral neuropathy, and nephrotoxicity.

The more common manifestations of injury to the nervous system are vestibular nerve dysfunction and neuromuscular blockade. Vertigo and ataxia usually do not appear until at least a total dose of 0.5 gm./kg. body weight has been given, although these symptoms may start after the first injection. Use of the drug should be stopped and bed rest with regular doses of prochlorperazine (10 mg. every four hours while awake) should be administered until the symptoms can be tolerated or disappear. Intraperitoneal, intrapleural, or rapid intravenous administration may result in curare-like neuromuscular blockage with respiratory paralysis and apnea. Streptomycin should not be used in anesthetized patients or those with myasthenia gravis. Neostigmine, 0.5 mg. or more intramuscularly, is the antidote of choice.

Sulfonamides

There are many different types and combinations of these synthetic antimicrobials. I prescribe *sulfadiazine* (nocardiosis and certain intestinal inflammations), *sulfisoxazole* and *sulfamethoxazole* (some genitourinary infections) and *trisulfapyrimidines* (toxoplasmosis) systemically. Precipitation of sulfonamide crystals in the renal tubules and pelvis has been no problem with these preparations if adequate hydration and an alkaline urine pH is maintained (with sodium bicarbonate if necessary).

Other toxic effects which may occur and require discontinuance of sulfonamide therapy include nausea, vomiting, dizziness, agranulocytosis, hepatitis, anemia (both hemolytic, in patients with G6PD deficiency, and aplastic), thrombocytopenic purpura, cyanosis (met- or sulfhemoglobinemia), photosensitivity, kernicterus in newborn infants by competing with bilirubin protein-binding, fever, hypoprothrombinemia,

polyarteritis nodosa, Stevens-Johnson syndrome (especially with the nonrecommended long-acting preparations), dermatitis, and anaphylaxis.[22]

The Tetracyclines

Because of their wide range of bacteriostatic antimicrobial activity and unusual toxic manifestations, the tetracyclines will be discussed separately.

Tetracycline, Oxytetracycline and Rolitetracycline. There is no added advantage to using chlortetracycline or demethylchlortetracycline in the treatment of any infectious disease. The former is less stable and the latter more toxic (photosensitization, anaphylactoid reactions, and nephrogenic diabetes insipidus) than the parent compound, tetracycline, or oxytetracycline. The following comments regarding tetracycline apply equally well to oxytetracycline, and there is no evidence that either one has any advantage in the treatment of infectious diseases or in the production of toxic effects in the adult.

Oral administration of tetracycline can cause the following minor toxic effects: nausea, vomiting, anorexia, epigastric distress, diarrhea, flatulence, and increase in stool bulk. Stomatitis, glossitis, vaginitis, and proctitis as a result of candidiasis may occur and are more common than with the use of antimicrobial agents of more limited application. Rashes and other manifestations of hypersensitivity rarely occur.

It is estimated that 50 per cent or less of the oral dose of tetracycline is absorbed, the rest remaining in the intestines. Because the bacterial population in the intestines may be so altered that vitamin K is not synthesized in adequate amounts, it is probably preferable that 5 mg. of vitamin K be administered orally each day while the patient is receiving one of the tetracyclines for longer than one week. Riboflavin deficiency is also a possibility and, with prolonged therapy, a multivitamin preparation should be given daily.

Tetracyclines can cross the placenta and affect the calcification of the deciduous teeth, a process which begins during the fourth month of gestation. A permanent disfiguring brown or yellow pigmentation may result, and it is recommended that tetracyclines not be given to pregnant women during the last two trimesters, or to children younger than 6 years of age. There is some evidence that oxytetracycline is less likely to produce these dental effects. An unusual toxic effect in the mouth is glossitis with atrophy of the filiform and enlargement of the fungiform papillae on the tongue (Fig. 2).

Amino-aciduria, hypokalemia, and other features of the Fanconi syndrome have been produced by degraded tetracycline as well as simulated systemic lupus erythematosus. This degradation is more likely to occur when the capsules have been improperly stored under conditions of extreme heat and humidity. Other rare toxic manifestations include benign intracranial hypertension causing bulging fontanelles in infants (reversible), transient myopia, and acute hemolytic anemia with thrombocytopenic purpura (oxytetracycline).

When administered to some patients with renal disease, tetracycline

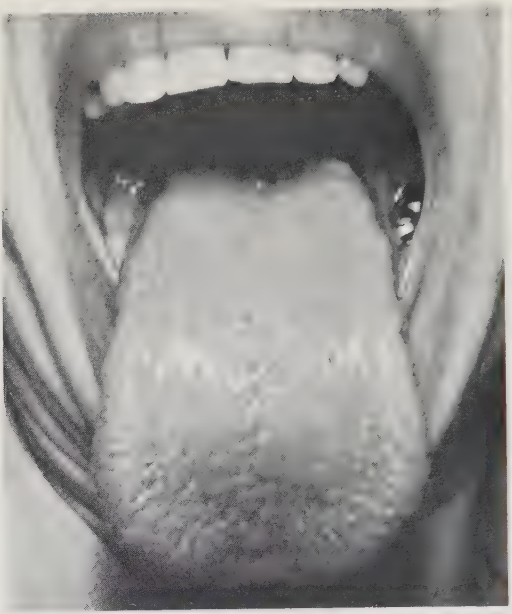

Figure 2. Glossitis with atrophy of filiform and enlargement of fungiform papillae of the tongue after tetracycline therapy. Condition recurred two years later with tetracycline therapy.

will produce an increase in blood urea nitrogen without a change in the creatinine level. It has been known that tetracyclines have a mild antianabolic effect in the patient with no renal disease, but this has not been a problem.[23] The dose of tetracycline should be altered for the rare patient with renal disease who requires this drug. It is recommended that after an initial loading dose of 0.5 gm. orally, 250 mg. should be given every six to eight hours if renal function is 75 per cent or more of normal, as estimated by creatinine clearance. If the creatinine clearance is 10 to 30 ml./min., a maintenance dose of 250 mg. should be given only once every two days.

Rolitetracycline, the preferred parenteral form of tetracycline, is usually administered in 350 mg. doses every 12 hours. Undesirable effects, which usually disappear within five to ten minutes after intravenous injection, include pruritus, flushing of the face, headache, dizziness, nausea, epigastric pain, and bitter taste, with or without an ethereal odor. The most serious toxic effect of parenteral use of tetracyclines is hepatic and pancreatic disease (occasionally fatal), which may occur if the recommended dose is exceeded or not adjusted when renal disease is present.

Despite the foregoing comments regarding toxicity of tetracycline, these complications occur rarely when the drug is administered properly, and tetracycline remains an outstanding antimicrobial agent. Death as a direct result of administration of tetracycline has been extremely rare.

CONCLUSIONS

Introduction of antimicrobial agents represents the greatest medical advance during the past hundred years, but unfortunately none of these

agents is a panacea for the cure of infection, and all are potentially toxic to man. It behooves the physician to be aware of the toxic effects of antimicrobial agents he uses, especially the life-threatening ones. Frequently, these effects are reversible if recognized promptly and therapy is altered accordingly.

GENERIC AND TRADE NAMES OF DRUGS

Alpha phenoxymethyl penicillin – penicillin V
Ampicillin – Omnipen, Penbritin, Polycillin
Benzathine penicillin – Bicillin, Permapen
Cephalothin – Keflin
Chloramphenicol – Chloromycetin
Chlorpromazine – Thorazine
Chlortetracycline – Aureomycin
Cloxacillin – Tegopen
Colistimethate – Coly-Mycin
Demethylchlortetracycline – Declomycin
Diphenhydramine – Benadryl
Erythromycin – Erythrocin, Ilotycin
Erythromycin estolate – Ilosone
Fungizone – Amphotericin B
Griseofulvin – Fulvicin-U/F, Grifulvin-V, Grisactin
Kanamycin – Kantrex
Levarterenol – Levophed
Lincomycin – Lincocin
Metaraminol – Aramine
Methicillin – Dimocillin-RT, Staphcillin
Nafcillin – Unipen
Nalidixic acid – NegGram
Neomycin – Mycifradin, Neobiotic
Neostigmine – Prostigmin
Nitrofurantoin – Furadantin
Novobiocin – Albamycin, Cathomycin
Oxacillin – Prostaphlin, Resistopen
Oxytetracycline – Terramycin
Penicillin G – Benzyl penicillin
Penicillin O – Cer-O-Cillin
Penicillinase – Neutrapen
Polymyxin B – Aerosporin
Prochlorperazine – Compazine
Rolitetracycline – Syntetrin
Sulfamethoxazole – Gantanol
Sulfisoxazole – Gantrisin
Tetracycline – many trade names
Triacetyloleandomycin – Cyclamycin, TAO
Trisulfapyrimidines – Terfonyl, Trisureid
Warfarin – Coumadin, Panwarfin, Prothromadin
Vancomycin – Vancocin

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Unusual Manifestations of Coronary Artery Disease

CHARLES B. MOORE, M.D.

Most patients consulting a physician because of pain in the chest eventually will be told that they have coronary artery disease. The primary reason for this is that thoracic pain and coronary artery disease are synonymous in the minds of most physicians. There may be valid reasons for such thinking. The distribution of pain in some patients with coronary artery disease is so unusual that accurate clinical assessment of the patient's complaints is extremely difficult. Also, and this fact is mentioned not because it is condoned, the physician who routinely makes a diagnosis of pain in the chest as being due to coronary artery disease may be erring on the side of caution. If the pain is due to some other cause, the "good physician" will be credited with having kept his "heart patient" alive for many years. On the other hand, if the patient does in truth have organic heart disease and dies after the diagnosis is made, at least the "astute physician" had prepared the patient and his family for this inevitable catastrophe. Not only is such practice intellectually dishonest, but it also creates many cardiac cripples who otherwise probably could lead normal lives. Although patients with coronary artery disease may have symptoms and electrocardiographic changes that are the same as those of patients with other abnormalities, with careful attention to detail the clinician can usually differentiate the unusual manifestations of coronary artery disease from other causes of pain in the chest.

USUAL CLINICAL MANIFESTATIONS

Four commonly recognized clinical syndromes are attributable to coronary artery disease.

Typical Angina Pectoris. The classical pain of angina pectoris is precordial or more likely substernal, oppressive, and heavy. It is related to increased myocardial work and consequently greater demand for coronary blood flow. The latter commonly occurs with physical exercise, such as walking, running, lifting, or climbing stairs, although

From the Department of Cardiology, Ochsner Clinic, New Orleans, Louisiana

it also occurs with emotional excitement (happiness, anger, or nightmares) or after ingestion of a large meal. Typically the pain is relieved upon cessation of the physical activity that has resulted in demand for increased myocardial blood flow. Typical anginal pain is relieved within five minutes by use of nitroglycerin sublingually.

CONGESTIVE HEART FAILURE. Left ventricular failure is usually a late manifestation of diffuse coronary artery disease in patients in whom myocardial hypertrophy has gradually developed and whose myocardial demands for nutrients have outstripped the coronary blood flow. The signs of left ventricular failure may include acute pulmonary edema or pulmonary hypertension and eventually right ventricular failure and evidence of systemic venous hypertension.

ARRHYTHMIAS. Various forms of cardiac arrhythmias due to coronary artery disease have been reported. The common forms are Adams-Stokes attacks secondary to complete atrioventricular block, presumably due to inadequate blood supply to the atrioventricular node; atrial fibrillation secondary to diminished atrial blood supply or to left atrial enlargement secondary to left ventricular failure; or various forms of potentially fatal ventricular arrhythmias, such as ventricular tachycardia or ventricular fibrillation.

ACUTE MYOCARDIAL INFARCTION. Probably the most commonly anticipated sequela of coronary artery disease is acute myocardial infarction due to coronary thrombosis. The potential hazards and complications of this condition are well known.

The foregoing manifestations of coronary artery disease are readily recognized by most physicians, and proper treatment usually is instituted promptly. Clinical aids in accurate diagnosis of these conditions vary. They include the history for angina pectoris, physical examination for the patient with congestive heart failure, and electrocardiography for patients with arrhythmias or acute myocardial infarction. These routine procedures may on occasion be supplemented by vectorcardiography, exercise electrocardiography, or special roentgenographic examinations in an effort to clarify the problem.

SELECTIVE CORONARY CINEANGIOGRAPHY

With the advent of adequate electronic equipment and proper technical skill in the performance of satisfactory selective coronary cineangiography, the problem of coronary artery disease is undergoing rapid change as more information is obtained concerning the anatomy of the larger coronary arteries. In more than 200 patients on whom selective coronary cineangiography has been performed at the Ochsner Clinic, it has become evident that there are at least four different groups of patients who formerly were labelled as having coronary artery disease, a diagnosis considered to be synonymous with atherosclerosis.

DEFINITE ATHEROSCLEROSIS IN MAJOR RAMIFICATIONS OF THE RIGHT OR LEFT CORONARY ARTERY. This group comprised the largest number of patients studied with abnormal coronary arteries. Demonstrated

abnormalities ranged from minor roughening of the intima to complete occlusion of one or more major coronary arteries.

Congenital Anomalies of the Coronary System. These anomalies appear to be more common than believed previously, and although most of them have no dynamic effect on myocardial blood flow, they may on occasion. Changes include origins of both right and left coronary arteries from a single sinus of Valsalva or origin of all coronaries from one ostium, rather tortuous and circuitous branching being necessary to supply adequate coronary blood flow to the more distal areas of the myocardium.

Microcirculatory Abnormalities. This group of patients cannot be clearly proved to have microcirculatory abnormalities by coronary cineangiography, since it is impossible to visualize the smaller vessels which presumably are involved. The clinical, electrocardiographic, and radiographic pictures suggest myocardial ischemia although major obstructive phenomena cannot be demonstrated. This condition has a predilection for patients with longstanding diabetes mellitus and can be definitely proved only at necropsy.

An Ill-Defined Group. In these patients the coronary arteries appear to be free of atherosclerotic involvement, and no apparent reason for microcirculatory abnormalities exists, but the coronary arteries are visualized as much smaller than normal and appear to be inadequate for the mass of myocardium which must be perfused. This condition occurs usually in patients with severe ventricular hypertrophy due to disease other than intrinsic coronary artery disease.

Because of this diversity of roentgenographic findings in the face of similar clinical pictures, coronary cineangiography has become a vital tool in the evaluation of patients who complain of pain in the chest. For this reason, coronary angiography is recommended in patients with typical angina pectoris who are being considered for myocardial revascularization; those with atypical pain in the chest in whom an accurate clinical diagnosis cannot be made; asymptomatic patients with unexplained abnormal electrocardiographic tracings; and patients who probably do not have coronary artery disease although such a diagnosis had been made elsewhere.

UNUSUAL CLINICAL MANIFESTATIONS

The unusual manifestations of coronary artery disease to be discussed are based on careful study of a large number of patients on whom routine tests plus ancillary procedures, such as exercise electrocardiography, vectorcardiography, and selective coronary cineangiography, were performed. In patients with obvious evidence of atherosclerosis of the major coronary arteries, the distribution of pain may be different from the typical precordial pain usually described in textbooks. Fairly frequent atypical locations are one or both elbows or the mandible; rarely, the fourth and fifth digits of the right or left hand are painful. Pain in these locations is not always easily explained on a neurologic basis.

Most patients with pain in such atypical sites say that if the physical activity or other precipitating factors are continued, pain eventually also develops substernally. Most patients, however, discontinue the activity causing the pain before substernal pain develops. The physician should realize that these apparently localized pains may be due to myocardial ischemia. Some patients have had teeth extracted for maxillary pain due to angina pectoris, and others have had steroid injections into elbows because of pain due to angina mistakenly diagnosed as bursitis.

Many patients with proved atherosclerotic disease of the major coronary vessels have complete occlusion of a major vessel but no definite electrocardiographic evidence of old transmural myocardial infarction. Many of these patients give no history of myocardial infarction. This coincides with the long-recognized examples of "silent" myocardial infarction discovered at necropsy in patients with no history of myocardial infarction. In many of these patients, good collateral bridging of the occluded area has been seen with adequate coronary blood flow distal to the occlusion supplied by these collateral vessels. Since this condition can be detected only by coronary cineangiography or postmortem examination, one may never be certain that the patient with normal results of indicated examinations does not have atherosclerotic disease of the major coronary vessels.

A third manifestation of occlusive disease of the major coronary arteries is paroxysmal nocturnal angina. This variant of left ventricular failure exists when, with assumption of the recumbent position and consequent mobilization of fluid from the dependent portions of the body, the left ventricle is called upon to perform more work and the coronary arteries are unable to supply the necessary increase in myocardial blood flow. The patient then experiences angina, which can be relieved by sitting up. This form of angina is identical to that of paroxysmal nocturnal dyspnea. It is the only type relieved by adequate salt restriction, digitalization, and use of diuretic agents.

Two other forms of angina pectoris have been described. The variant of the usual anginal picture described by Prinzmetal and associates[1] consists of fairly typical pain occurring regularly at the same time of day and associated with unusual electrocardiographic changes characterized by reciprocal ST elevation and depression. This type of angina is not relieved by administration of the usual medication for angina but does respond fairly well to administration of nylidrin hydrochloride.

Another variant of the anginal syndrome associated with atherosclerotic diseases of the coronary arteries is "second wind" angina. The patient with this type experiences angina with exertion but, with continuation of the activity at a given pace, his heart is able eventually to reach a steady state in which the coronary blood flow is adequate for the needs and the pain subsides.[2]

An attack of acute myocardial infarction secondary to coronary thrombosis will often completely relieve the patient with atherosclerotic coronary artery disease of the angina pectoris, since in most instances the vessel which becomes occluded is the same one which was pro-

ducing the myocardial ischemia and angina pectoris. As a corollary of this, if a patient continues to have angina after a myocardial infarction, it should be presumed that a second major vessel is also involved, and therefore, the prognosis is much poorer. Furthermore, certain complications of acute myocardial infarction are a direct result of the atherosclerotic process in the coronary artery. The four principal complications are:

Development of Ventricular Aneurysm. If the area of myocardial necrosis and subsequent scarring is sufficiently large, there will be an area of myocardium which, instead of contracting, will show a paradoxical motion or bulging out during systole. This is mechanically inefficient, since a major portion of the energy of the heart is expended in forcing blood into the aneurysm and back into the viable ventricular chamber. Surgical correction of this condition by aneurysmectomy results in miraculous improvement in hemodynamics. Fortunately for these patients, rupture of ventricular aneurysm is extremely rare.

Systemic Arterial Embolization. In the presence of transmural myocardial infarction, mural thrombi often develop on the endocardial surface at the site of the infarction, particularly if anticoagulant therapy is not used during the acute phase of the infarction. These mural thrombi may break off at any moment and act as systemic emboli passing to the brain, the peripheral arterial circulation, or even the coronary arteries themselves.

Intractable congestive heart failure may develop simply from lack of adequately functioning ventricular myocardium.

Finally, the infarcted ventricular septum may rupture. This complication can usually be easily diagnosed by development of a typical, harsh, loud, lower left sternal border systolic murmur and evidence of pulmonary plethora.

Most congenital abnormalities of the coronary arteries unassociated with atherosclerosis have no effect on the circulatory dynamics of the heart. These consist primarily in multiple unusual origins of the coronary arteries from a sinus of Valsalva. In certain instances these abnormalities may be of consequence. An occasional patient will have no right or left coronary artery—more commonly the right—and although the body attempts to supply the distal myocardium with blood, on occasion the supply is inadequate.

Another example of significant congenital abnormalities is the patient in whom one particular vessel has a major branch which comes off at the "bad" angle so that the pressure jet from the blood flowing down the coronary artery results in intimal trauma and eventual occlusion and subsequent myocardial infarction. The clinical picture would be identical to that produced by acute myocardial infarction secondary to atherosclerotic occlusion of a coronary artery, but cineangiography of the remaining coronary arteries reveals no demonstrable disease, and the prognosis can be presumed to be good. This phenomenon of bad branching has been well documented in the field of hydraulics and can be shown to be operable in certain young persons who have had acute myocardial infarctions.

A third example of congenital abnormality of the coronary arteries affecting the circulation is the patient in whom one coronary artery arises from the pulmonary artery rather than the aorta. This anomaly produces a functioning arteriovenous fistula with reversal of flow in the coronary artery arising from the pulmonary artery.

A final congenital anomaly of the coronary artery affecting the circulation is one in which one major orifice serves all coronary vessels, and the distal branches on the opposite side of the heart from the origin of the coronary artery are so far removed from their source of blood that "functional" inadequacy of the terminal vessels may exist. Patients with this anomaly are particularly vulnerable if atherosclerotic disease develops in the single large initial channel arising from the aorta, since the entire heart is supplied by one vessel.

In patients with microcirculatory abnormalities, coronary cineangiography is of benefit only in a negative sense. In other words, these patients have a history suggestive of coronary artery disease, abnormal electrocardiographic tracings, and frequently abnormal exercise electrocardiographic tracings; yet their coronary arteries are normal as far as they can be demonstrated by present angiographic techniques. The exact size of the vessel, which can be clearly seen, depends on specific aspects of film speed, image amplifier output, and several other technical factors. It is not yet possible to visualize the small vessels typically involved in patients with diabetes mellitus. Postmortem studies have shown, however, sufficient obstruction to flow in the small vessels may result in myocardial ischemia. The only clue to this diagnosis from the cineangiograms is poor "run off" of the dye from the major coronary arteries after injection, and this is difficult to quantify. Unfortunately, the technique of percutaneous myocardial biopsy has not been sufficiently perfected to recommend its performance in such cases. It is hoped that perfection of the recently developed methods of measuring coronary blood flow with radioactive xenon and surface-counting probes may help in recognizing patients with normal large vessels but considerably abnormal small vessels. At present the only reason for attempting to delineate this group from the previously mentioned groups is that attempted myocardial revascularization procedures are probably doomed to failure because of the location of the disease.

The last group to be considered is comprised of patients with an apparently inadequate number of coronary arteries for the myocardial mass. This is a heterogeneous group. Since it appears that the electrocardiographic pattern of left ventricular hypertrophy or strain is primarily an ischemic one, many patients with such conditions as aortic stenosis or longstanding essential hypertension will have anatomically normal coronary arteries which have been unable to compensate for the increased myocardial mass. A second group of great interest recently seen by us and others may well have a variant of congenital heart disease. Specifically, a number of young, otherwise healthy, women between the ages of 25 and 35 years, with normal menstrual periods, no diabetes, hypertension, hypercholesterolemia, myxedema, or other

predisposing factors of coronary artery disease, have had abnormal electrocardiographic tracings, exertional pain in the chest, and frequently abnormal exercise electrocardiographic tracings. In addition, most of them have recurrent attacks of paroxysmal atrial tachycardia, and in three of our seven patients, the Wolff-Parkinson-White type electrocardiographic conduction has been documented at one time or another. Again, on coronary cineangiography no evidence of atherosclerotic involvement of the coronary arteries is demonstrated, but diminutive, smooth, normal, healthy appearing coronary arteries with a caliber of lumen much smaller than one would anticipate for the size of the heart and with fewer visible major branches are demonstrated. The principal reason for delineating this group from women with overt atherosclerotic heart disease, is that they should be much more vulnerable to atherosclerosis at a later date, and it would therefore be advisable to attempt to prevent predisposing factors and particularly to prevent the menopause by judicious cyclic estrogen therapy at the proper time in their lives.

SUMMARY

Coronary artery disease and atherosclerosis are not synonymous. The typical patient with atherosclerotic involvement of the coronary arteries may complain of patterns and distributions of pain not normally considered to be those of cardiac origin. Numerous variants of the anginal syndrome secondary to atherosclerotic involvement of the coronary arteries occur, and careful attention to the history is necessary to delineate these from other causes of pain in the chest. By use of coronary cineangiography in evaluation of patients with pain in the chest, the clinician may differentiate atherosclerotic involvement of the major coronary vessels, congenital abnormalities of the coronary vessels, microcirculatory abnormalities of the coronary circulation (by inference), and apparently normal but inadequate coronary arteries. Therapeutic and prognostic implications of such differentiation are obvious.

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Manifestations of Atrial Septal Defects

JERRY D. JORDAN, M.D.*

An opening in the atrial septum allows blood, normally destined for the systemic circulation, to reenter and recirculate through the pulmonary circuit. This volume overload of the lesser circulation produces variable clinical manifestations during life from infancy to old age. It is the one congenital cardiac defect that is frequently compatible with survival to adulthood without development of symptoms,[8] and accordingly is often overlooked in childhood. Although it is the most common congenital cardiac defect in adults,[12] its unusual natural history and clinical manifestations frequently result in an erroneous diagnosis of acquired heart disease.

EMBRYOLOGY AND ANATOMY

During the second month of fetal life, partitioning of the upper chamber of the heart into right and left sides begins by growth of two septa. The first septum, or septum primum, begins on the dorsal cephalic portion of the atrium and grows toward the atrioventricular canal. The opening in the lower portion of this septum is known as the ostium primum, and with further growth of this septum, this opening is obliterated. Before its obliteration, however, the uppermost portion of the septum is absorbed and produces an opening, the ostium secundum. As this is taking place, growth of the second septum, or septum secundum, has begun; this septum grows in a dorsal caudal direction. This septum never completely develops; the remaining opening and the ostium secundum have a flat valve arrangement which forms the valve-competent foramen ovale.

Failure of complete growth of the septum primum results in ostium primum atrial septal defects, whereas excessive absorption of the septum primum or defective growth of the septum secundum results in the ostium secundum type of atrial defect. This discussion will be limited to the latter type, which is the most common. The most frequent location of the secundum defect is in the region of the foramen ovale. Because of excessive absorption or defective growth, however, a defect

From the Section on Pediatric Cardiology, Ochsner Clinic, New Orleans, Louisiana

may occur in the area superior to the foramen ovale and near the orifice of the superior vena cava. Defects in this location are known as sinus venosus defects. Similarly, abnormal absorption may occur posteriorly to the foramen ovale and involve the orifice of the inferior vena cava. These unusual locations produce no clinical manifestations different from those of the foramen ovale defect; however, they are of great significance to the surgeon, who must exercise extreme care in their closure to prevent obstruction to vena caval flow.

Another unusual kind of atrial communication is an acquired type. Kuzman and Yuskis[5] called it the "reversed Lutembacher's syndrome." They believed that prolonged mitral insufficiency or stenosis may, through the years, produce incompetency of the foramen ovale with resultant left-to-right shunt.

SYMPTOMS AND NATURAL HISTORY

To stereotype the patient with an atrial septal defect as one known to have had a heart murmur in childhood but no symptoms, except possibly difficulty in gaining weight and frequent infections of the respiratory tract, with development of congestive heart failure during the third or fourth decade of life, would be erroneous. The increasing interest in congenital heart disease, coupled with the ability to establish a diagnosis by cardiac catheterization, has brought forth uncontestable evidence that this anomaly has, perhaps, the broadest variations in its natural course.

At one time, it was thought that atrial septal defects had a completely benign course in infancy and childhood. In 1962, Hastrieter and co-workers[4] reported 13 cases of infants with uncomplicated atrial septal defects who had congestive heart failure. Their report was followed by others,[10] and the lethal nature of uncomplicated atrial septal defects in infancy was verified by Adams,[1] who collected 51 cases in which death occurred before two years of age, 40 during the first six months of life from pulmonary hypertension, congestive heart failure, and pneumonia. No infants with atrial septal defects and congestive heart failure seen at Ochsner Clinic have died. Figure 1 is the roentgenogram of a 5-month-old infant who had moderately severe congestive heart failure, and an isolated atrial septal defect of the secundum type was demonstrated by catheterization and angiocardiography.

Although uncommon, congestive heart failure also occurs in childhood. Weinberg and associates[11] reported five cases in children ranging from 1½ to 9 years of age. Figure 2 is the roentgenogram of a 7-year-old boy with an atrial septal defect. Cardiac enlargement, hepatomegaly, and exertional fatigue were present. Dramatic changes followed surgical correction. Weinberg and co-workers indicated that mitral valve disturbances or possible underdevelopment of the left ventricle may somehow influence development of symptoms in children.

After 30 years of age, symptoms are, of course, more frequent and more severe, the average life expectancy of patients with atrial septal

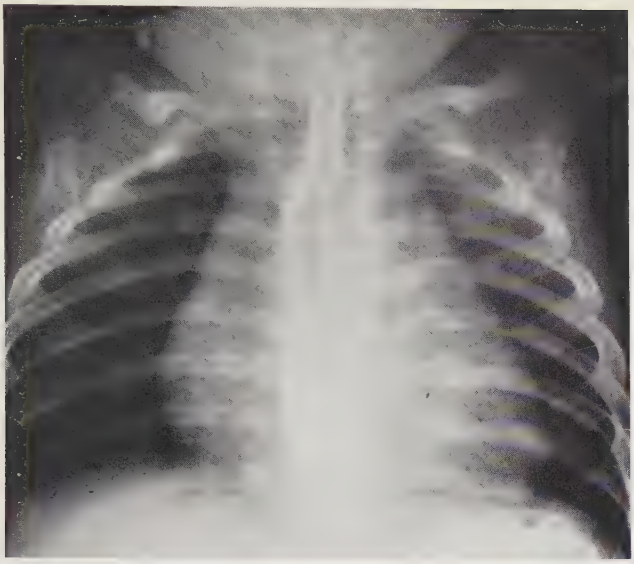

Figure 1. Roentgenogram of chest of 5-month-old baby boy with isolated atrial septal defect, no pulmonary arterial hypertension, and moderate congestive heart failure.

defects being 35 to 40 years. The symptoms at this age are usually those due to congestive heart failure and pulmonary hypertension. Cardiac arrhythmias, especially paroxysmal atrial tachycardia and atrial fibrillation, are common. Paradoxical embolization, although rare, may be manifested as an unexplained stroke, and the underlying heart defect may be overlooked. Also, because symptoms occur more commonly in the older age group, this anomaly is frequently misdiagnosed as acquired heart disease.

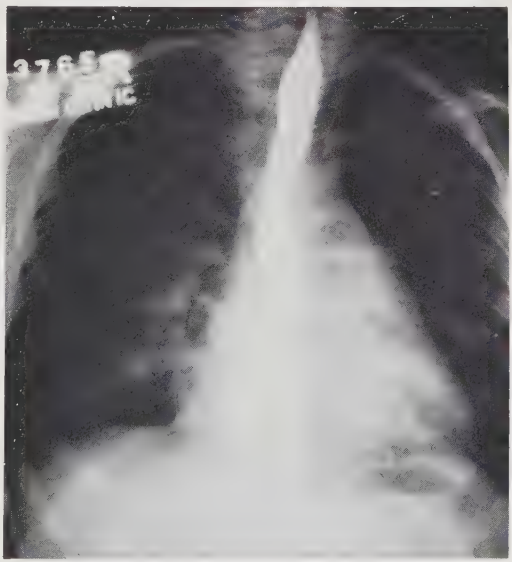

Figure 2. Roentgenogram of chest of a 7-year-old boy with isolated atrial septal defect and typical roentgenographic abnormalities of cardiomegaly, prominent pulmonary artery, and increased pulmonary vascularity.

Contrary to the foregoing occurrences is the frequent asymptomatic course a patient with an atrial septal defect may have even until the seventh or eighth decade of life. An atrial septal defect may not even be suspected in the infant or young child, because of absence not only of symptoms, but also of a heart murmur. In 23 per cent of one series of patients with atrial septal defects, no murmur was detected until five years of age.[3] An atrial defect is frequently first recognized at routine preschool physical examination. Not only may these children be asymptomatic but their growth and development may be normal. In a randomly selected series of 30 patients at the Ochsner Clinic, ranging in age from 2 to 18 years, with proved atrial septal defects, only 16 per cent were below the 18 percentile, whereas 23 per cent were above the 94 percentile. Forty of 92 patients with atrial septal defects, rated two plus severity hemodynamically by the study of the American Heart Association Committee on Rheumatic Heart Disease and Congenital Heart Defects, were asymptomatic.[13] This lack of correlation between symptoms and physiologic disturbances is further emphasized by the fact that patients 50 to 84 years of age with large defects had little cardiac disability.

The variability of symptoms remains unexplained. Also, it is impossible to render a prognosis in a particular patient with an atrial septal defect. It is generally accepted that the direction and magnitude of the shunt through the defect are unrelated to the pressure difference between the two atria but are due to the resistance to filling of the right and left ventricles, which is a function of the compliance and distensibility of these latter chambers.

In a newborn infant, right ventricular mass and thickness are approximately the same as those of the left ventricle; therefore, the distensibility of both ventricles is approximately equal, and accordingly little shunt across the atrial septal defect occurs, and no symptoms develop suggesting the presence of a defect. With "maturation" of the right ventricle into a thin-walled volume pump, distensibility and compliance become greater, and an increasing left-to-right shunt occurs. If systemic cardiac output remains adequate, however, no symptoms develop. With advancing age, compliance of the left ventricle probably decreases with an even greater left-to-right shunt and decreased systemic cardiac output, or decompensation of the right ventricle, due to chronic volume overload, and symptoms become manifest in the third and fourth decade.

As the modality of compliance (simultaneous volume-pressure changes) is difficult to quantitate, so is it difficult to explain the variations, onset, and severity of symptoms. Perhaps, in an occasional infant, the compliance of the right ventricle changes abruptly with production of a large left-to-right shunt followed by right ventricular decompensation, or even more likely, the left ventricle may have been poorly developed and therefore distinctly less compliant with resultant production of a greater left-to-right shunt at the atrial level and also decreased systemic cardiac output. Some infants having congestive heart failure and an atrial septal defect have pulmonary hypertension. This elevation

in blood pressure may be due to persistence of the fetal pulmonary arteriolar pattern. Preferably, this condition should be called primary pulmonary hypertension with an associated atrial septal defect, and death should not be attributed to the defect. Congestive heart failure does occur, however, in infants with atrial septal defects without pulmonary hypertension, as in the case illustrated in Figure 1.

Pulmonary hypertension is the major complication of atrial septal defects in older patients. Its mechanism of production is unknown. I believe, as did Adams,[1] that it does not develop solely on the basis of large pulmonary blood flow. Other factors considered by Adams are recurrent pulmonary infection, pulmonary thrombi in situ, recurrent pulmonary emboli from thrombosis within the uterine vessels in women after delivery, decreased right ventricular output after right ventricular failure with stagnation of the pulmonary circulation and eventual formation of thrombi, and chronic pulmonary disease obliterating the vascular bed with formation of thrombi.

AUSCULTATION

The characteristic murmurs and altered heart sounds noted in this anomaly, unlike most cardiac disturbances, are produced not by the flow of blood through the defect but by the increased flow of blood through the lesser circulation. Because these murmurs are functional, the auscultatory phenomena in this defect not only may be different from patient to patient but also may change in a particular patient from day to day.

The most consistent sign in atrial septal defects is *persistent splitting of the second heart sound* throughout both phases of respiration and in various body positions. Closure of the pulmonic component of the second heart sound always occurs after aortic closure. This phenomenon is due to prolonged ejection of the excessive blood from the right ventricle into the pulmonary artery. There may be some correlation between the size of the shunt and the degree of splitting, although such correlation is not invariable. Furthermore, the degree of splitting is not "fixed," since it may vary from 0.01 to 0.02 second. Although these patients do have altered electrical systole, this phenomenon is not the cause of the persistent splitting of the second heart sound.[6] It may potentiate the splitting; however, the altered electrical disturbance persists after surgical correction whereas the splitting disappears immediately in most cases.

A basal *systolic ejection murmur* heard best over the pulmonic area and transmitted to the back is usually present in most patients with an atrial septal defect. This murmur is produced by excessive blood flow across the pulmonic valve (relative pulmonic stenosis) and by turbulence produced by the blood flowing into a dilated pulmonary artery which is usually present in this defect. The murmur has all the characteristics of the innocent functional pulmonic murmur heard in many children and adults. In addition to this murmur the torrential flow of blood across the tricuspid valve and into the right ventricle also

produces a low-pitched rumbling *mid-diastolic murmur* which is best heard at the low left sternal border. These murmurs, however, are not directly correlated to the size of the left-to-right shunt and change in intensity from patient to patient and from day to day. The increased tricuspid valve flow also prevents approximation of the leaflets during ventricular diastole; therefore, at the onset of ventricular systole, they are closed at such velocity of force that *the first sound is accentuated.*

Although the foregoing four auscultatory signs may not be present in all patients with atrial septal defects, they are the most characteristic signs produced by this defect, and their presence should always alert the examining physician to suspect this diagnosis rather than acquired heart disease.

Many other auscultatory phenomena are noted in patients with atrial septal defects, with or without the complications of pulmonary hypertension and congestive heart failure. A distinct *tricuspid opening snap* has been reported in patients with this anomaly.[2] It is a functional sound and should not suggest the diagnosis of acquired heart disease. With dilatation of the pulmonary artery, a *pulmonic ejection click* is frequently noted. This sound is much less common in children and young adults, although McKusick[9] believed that in no other single condition does an early systolic click occur more consistently than in atrial septal defects. *Splitting of the first heart sound* is a common sign due to delayed closure of the tricuspid valve. Lopez and co-workers[7] indicated that the combination of splitting and accentuation of the tricuspid component of the apical first sound is a more useful indication of an uncomplicated atrial septal defect than is realized. Kuzman and Yuskis[5] reported an *apical pan-systolic murmur* characteristic of mitral insufficiency in six elderly patients with atrial septal defects; they consider this to be functional mitral insufficiency. Likewise, with onset of right ventricular failure, frequently the *murmur of tricuspid insufficiency* develops without true valvular disease. With onset of pulmonary hypertension, the *murmur of functional pulmonary insufficiency*, an early diastolic basal high-pitched murmur, may be heard. These uncharacteristic murmurs of atrial septal defects frequently lead to a misdiagnosis of acquired rather than congenital heart disease.

ROENTGENOLOGY AND ELECTROCARDIOGRAPHY

The roentgenographic observations in atrial septal defect may or may not reflect the severity of the disease, and at times they may suggest a diagnosis not only of acquired heart disease but also of something other than heart disease.

Since the physical signs are produced by increased flow of blood through the lesser circulation, the same disturbance produces the characteristic radiographic observations (Fig. 2). There is usually right ventricular dilatation with prominence of the pulmonary artery and increased pulmonary vascularity. The right atrium is enlarged, but this usually cannot be detected roentgenologically. The left atrium is never

enlarged. A larger left-to-right shunt usually accentuates these observations. The American Heart Association study,[13] mentioned earlier, clearly showed that there was no strict correlation between radiographic and hemodynamic observations, and some patients with a large shunt do not have cardiomegaly. Figure 3 is the roentgenogram of an 11-year-old boy with a proved atrial septal defect and normal heart size.

In the older patient with congestive heart failure, massive cardiomegaly occurs. The radiographic observations suggest acquired heart disease, such as arteriosclerotic or chronic rheumatic heart disease. Isolated massive dilatation of the pulmonary artery may occur in patients with this defect, so that a diagnosis of primary pulmonary hypertension may be considered. Of equal importance are the unusual hilar shadows produced on the roentgenogram by dilatation of the branches of the pulmonary artery. Figure 4 is the roentgenogram of one of two patients who were recently referred to us with a diagnosis of pulmonary cancer. Both were proved to have ostium secundum atrial septal defects, which were surgically corrected.

Incomplete right bundle-branch block, focal intraventricular conduction defects, delayed cristal depolarization, and right ventricular diastolic overload are a few of the terms used to describe the QRS pattern seen in the right ventricular leads in patients with atrial septal defects. In this defect the usual pattern is an rsR′ complex; however, rsi′, rsr's′, RS, and others may be noted. That this is a manifestation of hypertrophy or dilatation and not conduction disturbance is now well accepted.

In the differentiation of ostium secundum from ostium primum defects, the mean QRS axis on the frontal plane is perhaps the most

Figure 3. Roentgenogram of an 11-year-old boy with isolated atrial septal defect and pulmonary blood flow 2.5 times systemic blood flow demonstrating no cardiomegaly.

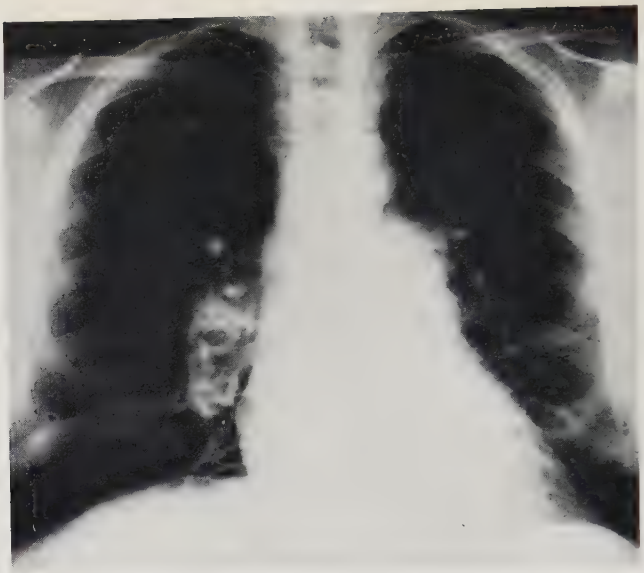

Figure 4. Roentgenogram of a 43-year-old man referred with a diagnosis of cancer of the lung due to a right hilar mass. A diagnosis of isolated atrial septal defect proved by cardiac catheterization and angiocardiography.

informative, since ostium secundum effects usually have right axis deviation and ostium primum, left axis deviation. Approximately 5 per cent of ostium secundum defects, however, will have left axis deviation. Unlike ostium primum defects, which involve the region of the atrioventricular nodes, the secundum defects usually have normal conduction and a normal PR interval. Arrhythmias are rare in the younger patient, but common in the older, and this anomaly should be considered in all older patients with unexplained episodes of paroxysmal atrial tachycardia or atrial fibrillation.

CONCLUSIONS

To consider any manifestation of an atrial septal defect as unusual is perhaps erroneous. The clinical manifestations of this defect are more varied than are those of any other congenital cardiac anomaly. Once this defect is considered as a possibility, the diagnosis is easily confirmed by appropriate cardiac catheterization and angiocardiographic study. The only treatment in patients without irreversible pulmonary arteriolar damage is surgical closure. The unpredictable natural history, however, makes it apparent that all patients with an atrial septal defect do not require surgical correction. Surgical techniques have been so developed that in most centers the surgical mortality rate is less than 1 per cent. During the past four years, no deaths have occurred after open heart surgical correction of atrial septal defects in 50 consecutive patients at Ochsner Foundation Hospital. Furthermore, surgical correction com-

pletely restores the heart to normal. Therefore, the clinician should not be reluctant to recommend surgical intervention to any of these patients.

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"Stiff Heart" Syndrome

An Uncommon Cause of Heart Failure

T. R. KILPATRICK, M.D.*

HAROLD M. HORACK, M.D.

CHARLES B. MOORE. M.D.

The commonly encountered causes of heart failure (coronary arteriosclerosis; pulmonary, hypertensive, valvular, and congenital heart diseases; myocarditis; and diseases characterized by high cardiac output) result from mechanical overload with or without myocardial dysfunction or destruction of fibers.[6] The term "stiff heart" has evolved to describe a group of cardiac diseases characterized by "restrictive hemodynamics." This phenomenon may be defined as alterations of cardiac function brought about by any pathologic process which renders the myocardial fibers abnormally rigid or externally applies a constricting pressure, and as a consequence, impedes flow of blood into the ventricular cavities. These changes in hemodynamic parameters are revealed only by cardiac catheterization. The clinical features of this syndrome are characteristic. The relative infrequency of its occurrence might well allow error in diagnosis to favor the more common causes of heart failure unless the possibility of this diagnosis is considered.[8] Its clinical picture is probably best described by report of the following case.

Report of Case

A 58-year-old white woman was referred to Ochsner Foundation Hospital May 20, 1966, for evaluation of increasing dyspnea of five months' duration. Her illness began in November, 1965, with pneumonitis, which required hospitalization. In mid December, 1965, fever, chills and a productive cough reappeared but responded favorably and promptly to antibiotic therapy. Exertional dyspnea developed during the last week of December, 1965, and gradually increased in severity during the next four weeks, but always was relieved by rest regardless of the position the patient assumed. By the first week of February, 1966, pretibial edema had become persistent. Digitalization resulted in little improvement. Paradoxically, during the five months that peripheral edema was accumulating

From the Section on Cardiology, Ochsner Clinic, New Orleans, Louisiana

*Present address, 134 N. 79th Street, Baton Rouge, Louisiana

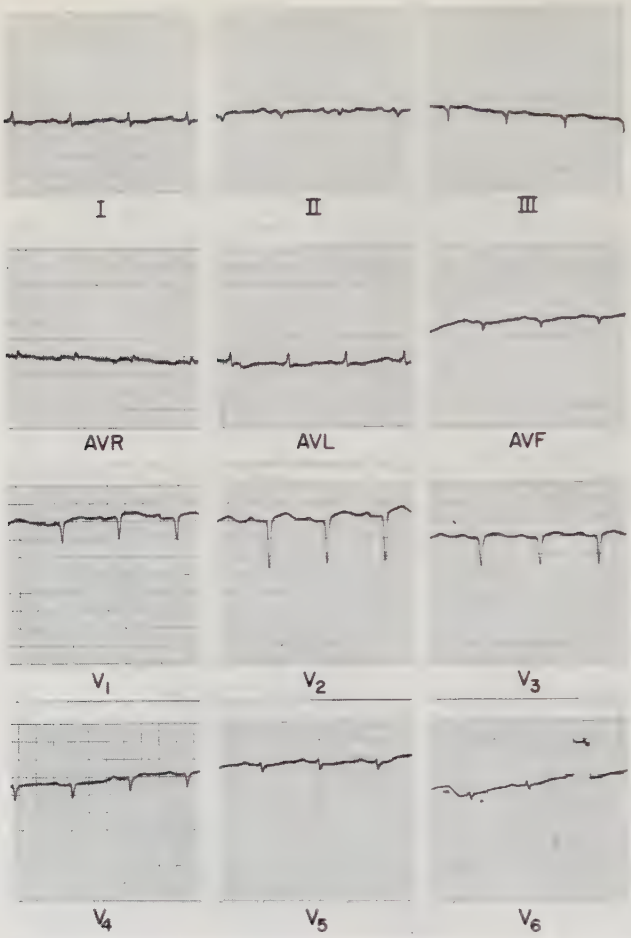

Figure 1. Electrocardiogram made on admission shows low voltage of the QRS complex in the standard and augmented unipolar limb leads; the Q waves in leads II, III, a VF, V_1, V_2, and V_3 were indicative of old posterior and anterior myocardial infarcts.

the patient lost 30 pounds. Interestingly, orthopnea did not appear until approximately one month before admission to this institution. To her knowledge, she had never had hypertension or pain in the chest. Two years before onset of the present illness, she had been found to have mild diabetes, which was easily controlled by dietary restriction. There was no strong family history of cardiovascular disease.

On admission, the patient appeared acutely ill and debilitated. She was afebrile, her blood pressure measured 120/75 mm. Hg, pulse rate 90/min., and respiration 18/min. Venous distention in the neck was impressive and changed little with inspiration. Breath sounds were diminished bilaterally, and no rales or rubs were heard. Percussion dullness was present in the left base posteriorly. The heart sounds were distant, the aortic and pulmonary second sounds being of approximately equal intensity. A diastolic gallop was heard, but no murmurs or friction rubs could be identified. Moderately advanced ascites obscured adequate evaluation of the hepatomegaly detectable only by ballotment. Peripheral edema reached the presacral area. She had no cyanosis, clubbing of the digits, or dermal pigmentations.

Results of complete blood count, erythrocyte sedimentation rare, urinalysis, Kahn and Kolmer tests for syphilis. serum cholesterol, fasting blood sugar, protein bound iodine, and L.E. cell preparations were all within normal limits. Serum proteins measured 5.5 gm./100 ml. (normal range 6.0 to 8.0 gm./100 ml.) with 4.1 gm. of albumin. The alkaline phosphatase level was 17.6 King Armstrong units (normal range 4 to 34 units), and the serum glutamic pyruvic transaminase was 39 Karmen units (normal range 4 to 34 units). The serum sodium concentration was 134 mEq./L., serum potassium 4.2 mEq./L., serum bicarbonate 27 mEq./L., serum chloride 90 mEq./L., and blood urea nitrogen 27 mg./100 ml.

The electrocardiogram showed low voltage of the QRS complex in the standard and augumented unipolar limb leads; the Q waves in leads II, III, aVF, V_1, V_2, and V_3 were indicative of old posterior and anterior myocardial infarcts (Fig. 1). The globular appearance of the cardiac silhouette in the roentgenogram of the chest was suggestive of pericardial effusion; small pleural effusions were present bilaterally, and pulmonary vascular markings were not accentuated (Fig. 2).

Although the patient's pulsus paradoxus measured only 8 mm. Hg (upper limits of normal), a diagnosis of "stiff heart" syndrome was strongly suspected because of the absence of dyspnea in the supine position, the presence of a diastolic third heart sound, and the poor response to digitilization. Cardiac catheterization (Fig. 3,II) confirmed the diagnosis. A plateau in the diastolic pressure existed from the right atrial mean pressure to the right ventricular end-diastolic pressure to the pulmonary capillary mean pressure. This plateau, designated by the letter P, is characteristic of restrictive hemodynamics. An exaggerated early diastolic dip also characterizes this syndrome and has been labeled d in tracing No. 2. If the early diastolic dip, d, and the late diastolic pressure plateau, P, are combined, the "square root" sign is made. In Figure 3 this patient's pressure tracings are compared with those of a normal heart and a patient with left heart failure due to coronary artery atherosclerosis. Selective coronary angiography revealed normal major branches of both coronary arteries. Carbon dioxide negative contrast studies were not done, but no thickening of the myocardial wall was suspected from cineangiograms made with positive contrast media. Rectal biopsy provided no additional information, including no amyloid material on staining.

In an effort to establish a more precise diagnosis, exploratory thoracotomy was done on May 25, 1966. Since no surgically correctable disease was found, ventricular biopsies were obtained. Histologic evaluation of this tissue revealed only nonspecific fibrosis and loss of myocardial fibers. On staining again no

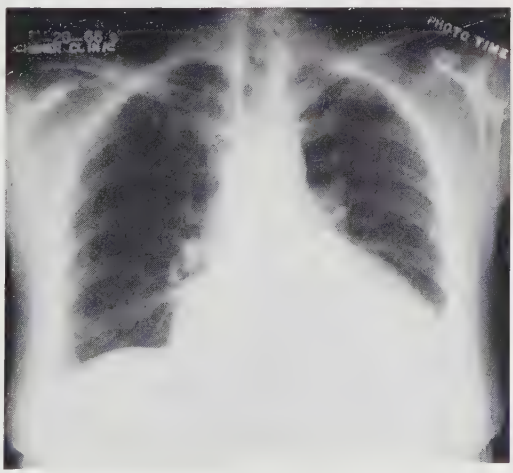

Figure 2. The globular appearance of the cardiac silhouette in the roentgenogram of the chest made on admission is suggestive of pericardial effusion; small pleural effusions were present bilaterally, and pulmonary vascular markings were not accentuated.

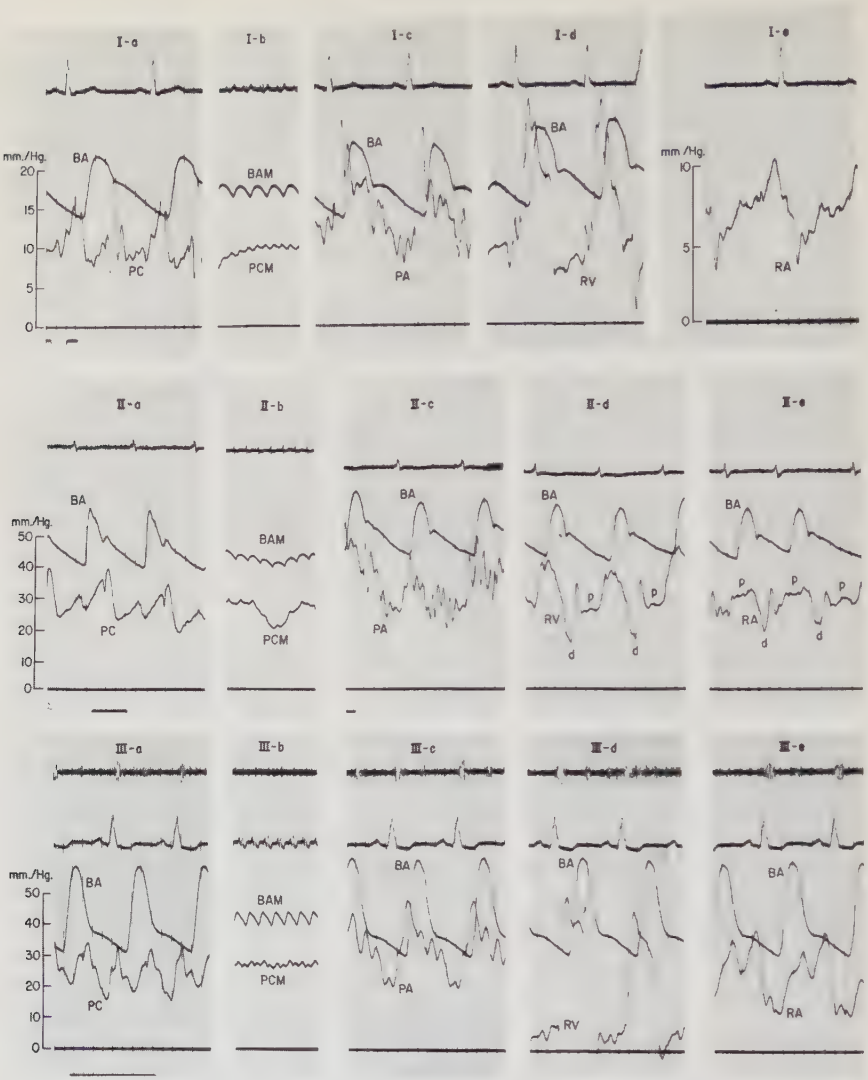

Figure 3. Comparative right heart catheterization. Tracing I is from a normal heart, tracing II is from the case herein reported and represents a typical "stiff heart," and tracing III is from a patient with congestive heart failure due to coronary atherosclerosis. BA = brachial artery. PCM = pulmonary capillary mean. RV = right ventricle. RAM = right atrial mean.

amyloid material was found. The heart failure continued to be refractory to all treatment, and on June 5, 1966, the patient died.

Necropsy. Small transudates were present in both pleural cavities, and approximately 30 ml. of the same type of fluid was present in the pericardial cavity. The heart weighed 410 gm., had only minimal atherosclerotic changes in the coronary artery, and had well preserved valves. Primary cardiac amyloidosis was established on microscopic examination (Figs. 4, 5). No amyloid material could be found on extensive search in other tissues.

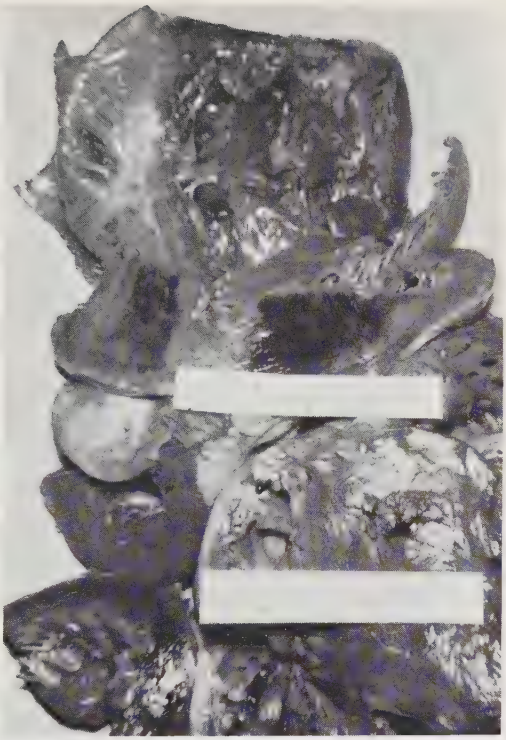

Figure 4. Positive evidence of cardiac amyloidosis on iodine stain on patient's heart in upper half of picture. Normal appearance of an iodine stain on another heart in the lower half of picture.

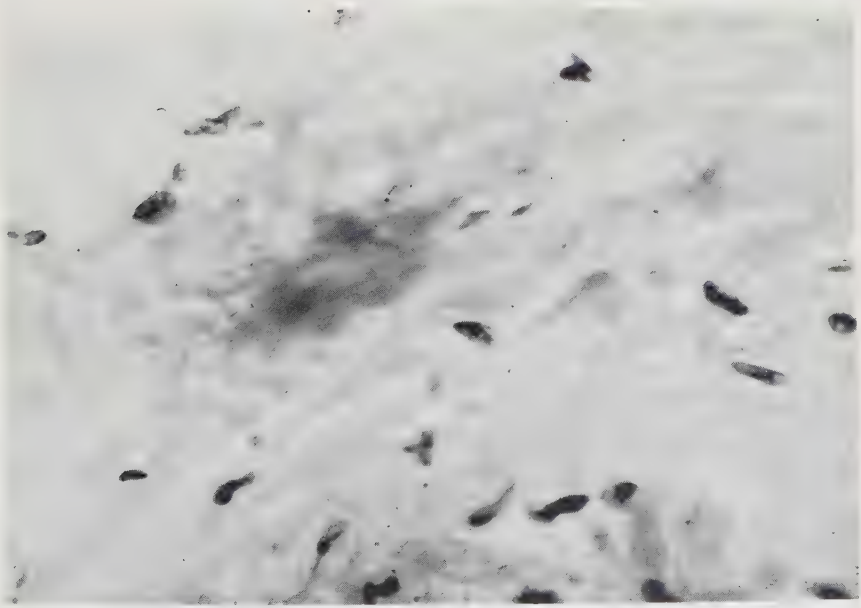

Figure 5. On Congo red stain examination, positive evidence of amyloid material noted (× 430). All other organs showed no amyloid-like material except a few of the smaller pulmonary arteries.

DISCUSSION

The causes of "stiff heart" syndrome can be divided into pericardial[4, 9] and myocardial.[5] The classical picture is chronic constrictive pericarditis. Tuberculosis has been its most common cause in past years, but as modern medicine has brought this disease under better control, other modern advances have brought other etiologic agents into a more prominent role. Excessive radiation and direct or indirect trauma to the chest can lead to this disease. Other causes include histoplasmosis, actinomyocosis, rheumatoid arthritis, and idiopathic pericarditis. Another pericardial disease, chronic pericardial effusion, usually does not result in restrictive hemodynamics but attracts attention by the alterations it produces in the cardiac silhouette on roentgenography of the chest. Tuberculosis also has been its most common cause in past years and usually is associated with bloody effusion similar to that produced by neoplasms. Lupus erythematosus and lupoid states induced by drugs like hydralazine, scleroderma, and idiopathic pericarditis also can produce pericardial effusions which are transudates. Interestingly, the pericardial effusion due to myxedema has not been reported to have been associated with cardiac tamponade.

Goodman and associates[5] collected 66 cases of primary and secondary myocardiopathies, which they classified into three groups; only four cases were classified as restrictive cardiomyopathy. Myocardial fibrosis of multiple causes and subendocardial fibroelastosis can result in a "stiff heart" syndrome. Becker's subendocardial fibroelastosis (South African cardiomyopathy)[11] and infantile subendocardial fibroelastosis[3] are not associated with restrictive hemodynamics, but both are characterized by progressive cardiac dilation. Loeffler's subendocardial fibroelastosis, however, is associated with restrictive hemodynamics, the subendocardial fibrosis usually involving the left ventricle. This entity is characterized by peripheral eosinophilia, which roughly correlates with the level of pathologic activity in the subendocardial tissues. The cause, however, remains obscure. In contrast to the first two types of subendocardial fibroelastosis, the size of the heart remains normal in the Loeffler type. Periarteritis nodosa, coronary arterial insufficiency, and myocarditis of many causes can all produce myocardial fibrosis capable of restricting cardiac function. Deposits of amyloid material in primary amyloidosis and hemosiderin pigment in hemosiderosis can produce a similar clinical and pathologic picture.

The *clinical picture* of "stiff heart" syndrome is similar to that of heart failure due to other causes, being characterized by exertional dyspnea until the late stages when orthopnea usually appears. Pain in the chest, typical or atypical for angina pectoris, may or may not be present. Elevation of systemic venous pressure is obvious and can be estimated by the height of the venous pulse above the sternum. Proficient examiners can interpret the rapidity of the X and Y descents of the jugular venous pulse which establishes obstruction at the superior vena cava or triscupid level.[12] Kussmaul's sign (increased distention of the cervical veins on inspiration) may be present but is not pathognomonic of a "stiff heart." Pulsus paradoxus (more than 8 mm. Hg differ-

ence in systolic blood pressure between inspiration and expiration) lends strong support to the diagnosis of a "stiff heart," but one must realize that certain diseases, such as pulmonary emphysema, can render the intrapleural pressure positive and thus produce pulsus paradoxus. Heart sounds are usually faint but can be of normal intensity. Additional diastolic sounds are common and are strong evidence of this diagnosis when present. Most examiners readily admit that phonocardiography is required to separate the slightly earlier "pericardial knock" of constrictive pericarditis from the ventricular gallop of the cardiomyopathies. The important thing to remember is that both of these sounds occur later than the pulmonary component of the second sound and the opening snap of mitral stenosis. The pulmonary fields are usually free of moist rales, presumably because of the reduction of systemic venous return and associated normal pulmonary vascular blood volume. Hepatomegaly, ascites, and peripheral edema are common; their extent depends on the severity of the disease.

The *electrocardiographic tracing* usually indicates some abnormality, although the result of this test can be normal. Complete electrical alternans occurs in congestive heart failure due to many causes and is of less diagnostic value. Atrial fibrillation appears more commonly in chronic constrictive pericarditis with abnormal Q waves, overt left ventricular hypertrophy, bundle branch block, supraventricular tachycardia, ventricular tachycardia, and varying degrees of atrioventricular heart block being more suggestive of cardiomyopathy.

In general, *radiographic techniques* have been more informative in the study of pericardial disease than of the cardiomyopathies. Classically, the cardiac silhouette of chronic pericardial effusion has a "water bottle" appearance. Measurement of thickness of epicardial fat pad from cineangiographic strips,[10] radioactive albumin heart scanning,[7] and negative contrast study with intravenous carbon dioxide[2] have all helped in appraising the thickness of heart chamber walls and estimating the amount of fluid in the pericardial cavity. Calcifications are common in chronic constrictive pericarditis, but the typical heart border "ring" is by no means diagnostic, since calcification of the coronary artery can closely mimic this picture. In both constrictive pericarditis and the restrictive cardiomyopathies, poor cardiac pulsation will be noted on fluoroscopy. Thus, a combination of poor cardiac pulsation and a ring of calcification along the border of a normal sized heart has to be taken as strong evidence of the presence of chronic constrictive pericarditis.

Cardiac catheterization will be required in most patients to substantiate the diagnosis of "stiff heart" syndrome. Pressure tracings should be obtained, as in our case, since a diagnostic pattern will be obtained in all cases. Even though this pattern is diagnostic of a "stiff heart" syndrome, it does not indicate a specific cause. Therefore, additional information usually will be required. Obviously, skin testing, sputum analysis, and detailed roentgenography of the chest should be done to detect tuberculosis and fungal diseases. Frequently, as in our case, pericardial fluid, pericardial tissue, or myocardial tissue will be needed. If only pericardial fluid is desired, percutaneous pericardio-

centesis can be done. If possible, this should be performed in a cardiac catheterization laboratory with continuous electrocardiographic monitoring of the exploring pericardial needle,[1, 9] unless the procedure is being done as a life-saving measure. Sometimes, limited exploratory thoracotomy will be required to obtain pericardial or myocardial tissue, or both. If tuberculosis is strongly suspected, antituberculosis therapy should be employed for several weeks before thoracotomy, since this has been shown to improve the chances of survival if a thick, tuberculous, pericardial rind has to be resected.

Phlebotomies reduce further the venous filling pressure and can be lethal to a patient with "stiff heart" syndrome. Since the pulmonary circulation has been spared from the excess vascular load, no physiologic reason exists for doing phlebotomy. Digitalization is probably of minimal benefit but is worthy of use. Adrenocortical steroids have induced excellent remissions in patients with polyarteritis nodosa and lupus erythematosus. Obviously, if hydralazine is being used and a lupoid state develops, use of this drug should be discontinued. Improvement has been reported in Loeffler's disease after use of diethylcarbamazine and arsenicals.[4] Pleuropericardial windows can be surgically created to drain chronic pericardial effusion. Unfortunately, the exact cause in some cases will not be determined, so that specific therapy cannot always be employed. Under such circumstances, the physician must resort to general supportive therapy.

SUMMARY

Since the "stiff heart" syndrome is uncommon, it can be mistaken for the more common causes of congestive heart failure. These causes have been classified into pericardial and myocardial. A typical case due to primary cardiac amyloidosis is presented.

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Essential Hypertension

OSCAR J. BIENVENU, JR., M.D.*

The *usual* manifestations of essential hypertension deserve perennial review by the practicing physician, because high blood pressure without recognizable cause is not thoroughly understood. Many denounce the word "disease" when applied to essential hypertension without organic cardiovascular sequelae.

Our interest is clinical, and so our attention is turned mainly to hypertensive cardiovascular disease (HCVD) or what we might call "severe hypertension." Even so, constant review and re-evaluation of the "facts" of these conditions are necessary, for these "facts" bearing on etiology, natural history, and treatment have not been absolutely settled.

For the sake of truth and research, our ignorances must be borne constantly in mind. For the sake of our patients, present statistics of the natural history of essential hypertension and of hypertensive cardiovascular disease must be ever in mind lest one mistreat, undertreat, or overtreat.

We are provided with a large and new armamentarium of medicines. Sadly, the mechanism of action of many of these drugs remains as obscure as does the cause of the condition itself.

Side reactions are seldom so resplendent as when reviewed from reports of treated hypertensive populations. These reactions range from the interestingly annoying to the morbid and even fatal. They constitute, for the demands of this topic, a main source of "unusual manifestations" of essential hypertension.

Indeed, the only other source from which one can draw for unusual manifestations is hypertension with known cause. Essential hypertension can mimic this type and pheochromocytoma, aldosteronism, and renal hypertension can mask as essential hypertension.

Systolic hypertension due to arteriosclerosis, the mild hypertension of hyperthyroidism (and other hyperactive states), and the hypertension due to arterial venous shunts and coarctation of the aorta may for a time be confused with essential hypertension. Hypertension may be produced by Cushing's disease and lesions of the central nervous system.

From the Section on Cardiology, Ochsner Clinic, New Orleans, Louisiana

The hypertension of pseudoxanthoma elasticum and Ehlers-Danlos syndrome, studied further, may some day yield knowledge of the pathogenesis of hypertension relating to the arterial wall itself.

The practitioner is interested in patients. It is therefore important to know all one can about hypertension, hypertensive cardiovascular disease, the action of drugs, and paradoxes that sometimes arise during the treatment.

NATURAL HISTORY

The onset of hypertension is usually insidious. Intermittent diastolic hypertension may precede constant elevation by months or years. The average duration of survival of the patient with hypertension from onset until death is 20 years, the hypertension being uncomplicated for three-fourths of this time. The blood pressures recorded under casual circumstances show little correlation with symptoms, rate of progression, or development of complications. About one-third of patients have no symptoms in the uncomplicated phase. Most patients complain intermittently of fatigue, nervousness, dizziness, weakness, insomnia, palpitation, or headaches, more often to a minor rather than a major degree. Headaches are mainly occipital or over the vertex. They are more apt to be present on awakening and rarely resemble migraine. Restlessness, emotional irritability, tachycardia, and flushing are fairly common, and an elevated metabolic rate without true hyperthyroidism may be encountered. Lability of blood pressure is evident in most persons during this phase.

Complications

It is said that concentric hypertrophy produces a relatively inadequate blood supply. Congestive heart failure is responsible for about 25 per cent of cases of hypertension with cardiac complications. About 10 per cent of patients get angina or die from myocardial infarction. Approximately 10 per cent suffer cerebral thrombosis or die from cerebral hemorrhage. In about one-half of hypertensive patients nephrosclerosis develops and is manifested clinically by polyuria and nocturia, diminished concentrating power, or proteinuria with or without the presence of red blood cells in the urine. In an occasional patient azotemia develops, resulting in death from uremia. Aneurysmal formation and rupture of the heart in myocardial infarction are more common in patients with hypertension.

In malignant hypertension pathologic alterations occur more rapidly with progressive renal damage, sometimes accompanied by retinal hemorrhages, encephalopathy, and papilledema. The clinical picture may be similar in occasional patients with severe nephrosclerosis as a result of progressive end-organ damage. The onset is abrupt whether or not preceded by established diastolic hypertension. Severe headache, blurring of vision, nausea, and loss of weight are common. Convulsions may occur. This hypertensive encephalopathy is *rarely*, if

ever, encountered in other phases of primary hypertension or hypertension without retinopathy. The sedimentation rate is elevated frequently. Slight alkalosis, hypokalemia, high aldosterone secretion, and high exchangeable sodium concentration are often found, probably related to *secondary* hyperaldosteronism. Cerebrospinal fluid pressure may be high unless the course is terminated along the way by complicating cerebral or cardiac damage. Renal damage progresses to azotemia, and death from uremia occurs in a considerable percentage of patients within two years.

A large number of hypertensive subjects will escape cardiovascular disease. Also, of those with organic changes, many will retain their physical and intellectual capacities for many years, unless disabled iatrogenically by cardiac neurosis. In terms of prognosis, the absolute value of keeping the blood pressure at a near-normal level has not been definitely settled.

Treatment

One need only read the succinct paragraphs of George A. Perera in Cecil's *Textbook of Medicine* to appreciate the best present attitude in treatment of hypertension. He reminds us that the cause cannot be removed, since it is not yet known, and that there is no convincing evidence that most of the pathologic changes can be blocked. Life can be prolonged in patients with malignant hypertension by appropriate management. One should remember, however, that many patients have hypertension; malignant hypertension, which to many modern writers is a different disease, is relatively rare. Counseling the patient is a vital duty. Relief of anxiety can substitute for much drug therapy. Patients can be taught to live with their disease. Interaction of personality, environment, and disease must be given attention. The action of drugs must be thoroughly appreciated.

ETIOLOGIC ASPECTS

Essential hypertension is more common in women than in men. It occurs in 5 per cent of the population of the United States. It is found in 10 per cent of patients with diabetes. The average age at which it can be detected is about 32, and some cases have been reported in childhood. Onset after 50 years of age is most unusual. The malignant form is more common in men. In the United States it is more common among Negroes. Women in whom malignant hypertension develops are lean, whereas most women with hypertension are obese. In only about 1 per cent of patients with essential hypertension does the malignant form develop. One-third of patients with the malignant form get the disease between the ages of 37 and 42 years.

Primary hypertension has been proved clearly to have a familial concentration, and there *is* justification for thinking along the lines of biochemical aberration or inborn error in metabolism.

Hypertension is often transient before it becomes permanent. When it becomes permanent it may or may not produce disease. The specific pathologic alterations produced by hypertension are changes in the arteriolar wall and hypertrophy of the left side of the heart.

The blood pressure is determined by blood volume, cardiac output, blood viscosity, and peripheral resistance. Only peripheral resistance appears to be an important factor in hypertension and hypertensive cardiovascular disease. Major changes of these other factors are required to alter the blood pressure. Only minor changes in the caliber of the arterioles, however, are necessary to produce changes in the blood pressure.

However convincing the theories relating to mental, emotional, or personality changes as the cause of hypertension, it is generally agreed that overaction of sympathetic tone does not play a part in production of hypertension or hypertensive disease. This general line of investigation is not exhausted, however. Studies are now in progress attempting to relate changes in receptor and activator sites of the sympathetic system to pathogenesis.

No significant biochemical differences have been found in patients with essential hypertension and in persons with normal blood pressure. Although we have considerable knowledge regarding catecholamine metabolism, a specific abnormality in this regard is not found in patients with essential hypertension; yet an inborn error of metabolism is not excluded as the possible pathogenesis.

Mechanisms of control of the blood pressure stem largely from adrenergic enervation of blood vessels through such controls as carotid sinus moderator nerves, central and peripheral reflex centers, and chemical mediators such as epinephrine and norepinephrine. Respiration and venous return affect the blood pressure. Diastolic pressure is higher in the sitting or standing subject. The systolic pressure shows a transitory drop when the erect position is assumed. Pressure is lower during sleep. Exercise raises the systolic pressure. Emotional reactions, discomfort and pain, Valsalva's maneuver, and distended bladder affect the systolic pressure. Some persons have blood pressures of 170/100 with excitement or apprehension for years without ever showing objective signs of disease. The obese arm produces readings, when recorded by the sphygmomanometer, of 10 to 15 mm. above the true intra-arterial pressure. Rest, fever, and syncope reduce the blood pressure.

Vascular accidents, coronary or cerebral, may reduce to normal the established diastolic hypertension which the patient had before the attack for periods up to two years. The cause in most cases is obscure.

Most patients with diastolic hypertension show no appreciable change in cardiac output, blood volume or viscosity, pulse rate, circulation time, or venous pressure. Blood flows through the limbs, brain, and other areas at comparatively normal rates contrary to flow observed after epinephrine administration. Muscle blood flow may be increased however. Pressure in the pulmonary artery is usually normal. Patients with established diastolic hypertension excrete a greater proportion of a sodium load than do normal persons.

PROBLEMS RELATING TO HYPERTENSIVE DISEASE APART FROM ESSENTIAL HYPERTENSION

A patient with essential hypertension may have increased systolic pressure produced by severe anemia, thyrotoxicosis, beriberi, arteriovenous fistula, complete heart block, aortic insufficiency, or coarctation of the thoracic aorta.

Toxemia of Pregnancy

Toxemia of pregnancy is accompanied by hypertension. Its cause remains as obscure as that of essential hypertension. In this obscurity they may have more in common than we know. In toxemia of pregnancy retention of sodium and water develops followed by severe generalized vasoconstriction but no cause-and-effect relationship has been demonstrated. The diastolic pressure is usually increased comparatively more than the systolic pressure, and this may be responsible for a number of the cerebral and renal signs and symptoms which are characteristic of the condition. Treatment with the thiazide diuretics, if begun before development of vasoconstriction appears to decrease the likelihood of progression. For emergency situations in the patient whose blood pressure is high and in whom eclampsia is threatening, trimethaphan (Arfonad), which is always given intravenously, is probably the most generally effective single agent available for use. The onset of action is rapid, and its combined effects of ganglionic blockade and direct peripheral vasodilation can almost always lower the blood pressure. Its action is brief, and reliable control of the blood pressure requires minute-to-minute regulation of the rate of infusion.

Diazoxide, which produces fluid retention if used for extended periods, is effective in acute emergencies in pregnancy, and if used only for a short time, does not contribute to salt and water retention.

Coarctation of the Aorta

Coarctation of the aorta produces chiefly high systolic blood pressure. The diastolic pressure may be elevated to a variable degree. The mechanism of hypertension and coarctation is not clear. Experiments on animals suggest that it is not simply an obstructive phenomenon. Humoral and renal theories have been proposed for the cause of this hypertension.

Pheochromocytoma

Pheochromocytoma accounts for less than 0.1 per cent of cases of hypertension. It should be suspected if neurofibromatosis is present. In only half the cases is the hypertension truly intermittent or paroxysmal. When such is the case, however, the episodes complained of are pounding headaches, sweating, palpitation, apprehension, tremulousness, pallor, or flushing of the face, nausea and vomiting, pain in the chest and abdomen, and paresthesias in the extremities. Usually the pupils are dilated, and the limbs are cold. The patient is drenched with perspira-

tion. Hyperpyrexia may be present. These patients give paradoxic response to autonomic blocking agents; that is, to agents which block nerves at locations which result in receptors being oversensitive to norepinephrine. Phentolamine is an adrenergic blocking agent, and, of course, is an exception to this rule.

There are many histamine hyper-reactors in the essential hypertension population. The cold pressor test helps eliminate these. If a patient does have pheochromocytoma and histamine is given and produces an alarming response, 5 mg. of phentolamine (Regitine) should be administered intravenously. This is the same dose that is used for the Regitine test.

In essential hypertensives who have had myocardial infarction, catecholamine levels in the urine may be elevated. The same applies to patients with extensive burns.

The internist interested in hypertension who is consulted by surgeons should remember that after surgical removal of a pheochromocytoma the blood pressure may fall precipitiously to shock levels. Presurgical control of hypertension with phentolamine orally may obviate many such difficulties. Norepinephrine is a nearly specific drug; however, the extreme hypertension and vasoconstriction produced by the circulating catecholamines and stimulated to greater excess by the surgical procedure cause loss of fluid volume from the blood. Loss in the blood volume with accumulation of fluid in the tissues may require replacement of intravascular fluid to bring about a response from shock. In hypertensive patients who are admitted in a state of shock the possibility of a pheochromocytoma must be considered. The treatment would be as described. Patients with pheochromocytoma may have severe retinal changes. Some have orthostatic hypotension. Glycosuria may be intermittent. The basal metastatic rate is elevated in about half the patients. Pheochromocytoma should be suspected in all hypertensive and hypotensive reactions during anesthetization or pregnancy, in unexpected hypertensive and hypotensive reactions to antihypertensive agents, and in hypotension after administration of phenothiazine tranquilizers. These drugs cause a paradoxical response to circulating catecholamines. Among the commonly used phenothiazine tranquilizers are chlorpromazine (Thorazine) and thioridazine (Mellaril). Chlorpromazine has been shown to be an effective sympathetic blocking agent capable of producing vasodilation.

Sometimes the phentolamine test produces shock. Specific treatment is norepinephrine. Bananas and other fruits contain catecholamines and can spoil a urine collection for catecholamine content. Drugs such as reserpine and guanethidine, the antibiotics of wide application, methyldopa, and phenothiazine also interfere. The same is true for monamine oxidase inhibitors, disulfiram (Antabuse), coffee, and vanillin.

False-positive urine catecholamine collections are obtained in conditions other than pheochromocytoma, which increase secretion of catecholamines and their metabolites. A partial listing is hypoglycemia, thyrotoxicosis, angina pectoris, myocardial infarction, renal disease,

jaundice, lymphoma and brain tumor. Nose drops containing noncatecholamine derivatives may cause false-positive collections.

There is evidence that false-negative reactions with phentolamine are common in subjects who have been taking antihypertensive drugs during the preceding two weeks.

Hyperaldosteronism

Primary hyperaldosteronism results in hypertension, renal wasting of potassium, hypokalemia, and alkalosis. The common age of occurrence is between 40 and 50 years. The hypertension is usually mild, but there may be cardiomegaly and congestive heart failure, headache, vascular accidents, and occasional retinal changes—indeed, nearly all the signs associated with hypertension from any other cause.

The hypokalemia results in muscle weakness, even paralysis. Electrocardiographic changes associated with hypokalemia and rhythm disturbances are common. Nephropathy may be produced by hypokalemia.

The definitive diagnosis is made by demonstration of excessive adrenal secretion of aldosterone under physiologic conditions that normally do not invoke aldosterone secretion. Remember, normally, sodium depletion stimulates volume receptors that in turn stimulate the adrenal to secrete aldosterone and to conserve sodium. These volume receptors may be in the kidney, heart or major blood vessels, and cervical vessels. Also, renin, angiotensin, or both, may directly augment adrenal aldosterone production independently of the central nervous system.

To demonstrate pathologic elaboration of aldosterone, one must insure that there are optimal expansion of the body fluid and no sodium depletion. The patient is given adequate sodium intake, and diuretic agents are avoided. If there has been previous sodium depletion or diuretic therapy, a patient may be expected to exhibit elevated secretion of aldosterone. In addition, prolonged sodium depletion may correct all the secondary biochemical anomalies, including return of the low levels of serum potassium to normal, lowering of the serum pH and bicarbonate, and expansion of the body stores of potassium.

Patients with essential hypertension who have been treated with diuretics, especially orally, may have low serum potassium concentration and appear to have hyperaldosteronism. Patients with essential hypertension may have renal damage which, in fact, may cause secondary hyperaldosteronism. Unilateral renal ischemia, which produces hypertension, may mimic hyperaldosteronism.

Patients with essential hypertension who have been treated with diuretics and exhibit low serum potassium and elevated urinary potassium concentrations will show slow return to these values to normal if 150 mEq. of sodium is allowed daily. In primary hyperaldosteronism, however, the serum potassium concentration will drop further as urinary potassium increases. Patients with hyperaldosteronism seldom have edema. Edema in a given patient would suggest either that the patient has complicating heart failure or that the aldosteronism is due

to the disease causing the edema; that is, that secondary hyperaldosteronism is present.

The most frequent initial complaints of hyperaldosteronism are muscle weakness and polyuria. The muscle weakness may be chronic or episodic, and in most cases the weakness appears only after administration of a thiazide-type diuretic. The polyuria is believed to be due to nephropathy produced by potassium depletion. The nephropathy, however, is not specific for primary aldosteronism and may occur in association with any disease attended by significant total body potassium depletion. Elevation of the blood pressure is mild to moderate (160/100 to 200/120). Malignant progression is not characteristic. Retinopathy is usually mild. Cardiomegaly is reported in 40 per cent of cases, but usually congestive heart failure does not develop. The average serum potassium value is below 3 mEq./L.; however, some patients have these low levels only episodically. Alkalosis is manifested by elevated bicarbonate concentration of plasma and normal or elevated blood pH.

Hypernatremia is frequent but not consistent, and hyponatremia is virtually never present. Thiazide diuresis may deplete the extracellular fluid volume, and this depletion may stimulate increased urinary aldosterone secretion rate. This may give a false picture of hyperaldosteronism.

Patients for study should not have taken thiazide diuretics for several weeks before appropriate testing. In some patients, 15 mEq./L. of potassium chloride three times daily for several days should be given before the testing. On the other hand, as mentioned earlier, sodium depletion resulting from either diuretic therapy or dietary restriction may mask the electrolyte abnormalities of primary aldosteronism, and an adequate sodium allowance should be given when studying these patients.

Mentioned are formidable conceptual, as well as diagnostic, difficulties which may be encountered in the patient with malignant hypertension and secondary aldosteronism. The presence of malignant hypertension is, however, in itself strongly suggestive evidence that the patient does not have an aldosteronoma. Patients with malignant hypertension generally have less pronounced hypokalemia, 3.2 to 3.8 mEq./L. These patients usually have hyponatremia, a rare finding indeed in the patient with an adenoma. Reports of muscle weakness and polyuria are scant in the secondary group. Juvenile primary hyperaldosteronism, however, is more frequently accompanied by malignant hypertension. Potassium wasting renal disease in patients with hypertension rarely may serve as a source of confusion, but since most cases represent aberrant forms of Fanconi's syndrome or instances of primary renal tubular acidosis, evidence for other tubular defects, hyperchloremic acidosis, hypophosphatemia, hypouricemia, and renal glycosuria will be demonstrable. Patients with other forms of hyperadrenalism, Cushing's disease, or neoplasms with ACTH production will exhibit increased urinary 17-hydroxysteroids and 17-ketosteroid excretion rates. Ingestion of large amounts of licorice for a long period of time has been incriminated in the production of hypokalemic alkalosis and hypertension, with low aldosterone secretion.

More on Etiologic and Pathophysiologic Considerations

The clinician meeting problems in a disease whose cause is obscure and whose therapeutic rationale is also uncertain may profit by the following knowledge:

Section of the carotid sinus and depressor nerves will elevate the blood pressure and produce tachycardia and an increase in cardiac output. Local application of epinephrine and norepinephrine to these vessels will induce a fall in pressure. Infusions of epinephrine and norepinephrine produce elevation of blood pressure but only for a few days. Cortisone usually produces elevation of the blood pressure only if sodium is allowed.

SOME ASPECTS OF PATHOPHYSIOLOGY OF ABNORMAL BLOOD PRESSURE

The Goldblatt kidney produces renin, which, with hypertensinogen, forms angiotensin, which, in turn, produces high blood pressure through peripheral vasoconstriction. Angiotensin also increases the secretory rate of aldosterone from the adrenals. By this action, it produces sodium retention and antidiuresis in normal persons. In hypertensives, however, it produces a diuretic and naturetic response. The kidney is said to excrete angiotensin, and some forms of renal disease may produce hypertension as a result of failure of excretion of this material.

Most of these statements apply only to renal hypertension in its early phases. No clinically useful antidotes to increased renin formation have been developed. Continued elevation of serum angiotensin beyond the early phases of renal hypertension is not established.

The total cross-sectional area of all the arterioles of the body is not much greater than that of the aorta, but the surface area in contact with the blood which enhances the resistance to flow is enormous in comparison. The surface area and cross-sectional area of the systemic capillary bed are several hundred times that of the aorta.

Arterioles are normally in a state of partial constriction due to tonic activity of sympathetic vasoconstricting nerves which supply them. In mild bleeding, arterioles reflexly contract and maintain a steady systemic blood pressure, and this causes a decrease in capillary flow.

If a body is heated, the arterioles relax, offering less resistance to flow; and, at this time mean capillary pressure is raised as blood flows through the capillaries more quickly, and as such facilitates heat loss from the skin. The arterioles are also susceptible to chemical influence; thus in exercise local accumulation of metabolites causes severe arteriolar vasodilatation in the muscle, and blood pressure may be kept constant despite a fivefold increase in the cardiac output during the exercise.

Here are some figures for the distribution of cardiac output:

1. 1,300 cc. of blood flows through the kidneys per minute, 800 cc. flows through the brain, and perhaps 1,500 cc. through the liver.

2. The skeletal muscle and resting limbs receive 2 to 3 ml./100 ml. of muscle, and as there are about 30 kg. of muscle, 40 per cent of the body weight in a man of 70 kg. of muscle receives a total flow of 600 to

900 ml. Thus, 4,200 to 4,500 cc. of blood flow is accounted for; the remainder supplies the skin, bones, and intestine.

3. Skin flow depends largely on temperature. It may become high when the body temperature has risen. Most people are aware of the danger of taking a hot bath after a large meal, when vasodilatation of splanchnic and cutaneous beds may result in hypotension and syncope.

Hyperventilation causes fall in blood pressure, because the vasomotor center requires a certain CO_2 tension for normal function. CO_2 tension has opposite effects, however, when it is considered in terms of its action directly on the arterial wall. In man, then, hyperventilation seldom produces severe drop in blood pressure. The cutaneous vessels are constricted and the skin becomes cold and pale.

Reflexes

Reflex vasodilatation is occasioned by rises in blood pressure. When blood pressure falls, the tonic activity of the nerve endings is reduced and the vasomotor center escapes from afferent inhibition and thus causes increased sympathetic vasoconstrictor discharge. Reflex nerves then are best called "buffer nerves." Baroreceptors of the cardiovascular system exist in the carotid arteries, the aortic arch, and the root of the right subclavian artery, the right and left atria, the pulmonary artery, and the right and left ventricles.

Effects of Hemorrhage

Hemorrhage reduces the blood volume and causes a fall in the cardiac output, but reflex vasoconstriction secures an increase in peripheral resistance and a sequential reduction in the venous capacity. Since 70 per cent of the blood volume at any one moment is in the venous side of the circulation, reflex vasoconstriction provides a valuable reserve of blood for venous return. Similarly, organs with a reservoir function (skin, liver, and spleen) are affected by venous constriction which expresses blood from them toward the heart. The flow of blood is reduced by arteriolar resistance in the skin, splanchnic bed, and muscle, the less vital organs. Because of diminution in capillary pressure at this time, it is more likely that fluid will enter the circulation rather than leave it, and this accounts for increase in blood dilution due to hemorrhage. Hemodilution due to this mechanism is a reflex change and depends neither on the amount of blood lost nor on a fall in the mean blood pressure.

Grayish pallor of more severe shock is due to this sympathetic vasoconstriction, and hence reduced blood flow through the skin. The blood suffers excessive dioxygenation as its flow is so slow, and the grayish appearance may be attributed to the content of reduced hemoglobin in the blood contained in the capillaries and subpapillary venous plexus.

Cold sweat is due to sympathetic discharge affecting the sweat glands. Cold skin is due to vasoconstriction. "Goose pimples" are also the result of sympathetic discharge.

The thin, thready pulse is due to the reduced stroke volume of the

rapidly beating heart supplied with only a small venous return. Renal flow in hemorrhage is severely reduced as a result of decreased cardiac output and lowered arterial blood pressure combined with renal vasoconstriction. When the patient finally faints, it is because of unexplained sympathetic dilatation of the vessels in the skeletal muscles leading to collapse of the blood pressure. Also, unexplained slowing of the heart beat occurs at this point.

Shock

The clinical picture of inadequate circulation may be produced in many ways: inability of the heart to pump; failure of the heart to fill (because of pericardial tamponade or reduced venous return); obstruction of main arterial pathways, such as pulmonary arteries; widespread failure of cellular metabolism; and loss of vasoconstrictor tone, for example, endotoxin shock. In patients with small blood volume, the low blood pressure is produced by decrease in cardiac output, and arteriolar dilatation is *not* present. The pallor of the skin, coldness of the limbs, sweating, weak and thready pulse, narrowing of the field of consciousness, and restlessness are secondary to the diminished cardiac output and arteriolar reflex vasoconstriction. Thus arises the theory that vasodilators might help correct, in part, in pathophysiology of shock.

Nitroglycerin may produce hypotension due to pooling of blood in the peripheral veins, and syncope may occur in susceptible patients.

In essential hypertension, the cardiac output, capillary and venous pressures, and blood viscosity are all normal. This and other observations tend to show that hypertension is the result of arteriolar narrowing. Circulatory response to carotid sinus compression and carotid occlusion appears to be normal. Adaptation occurs so that the sinoaortic baroreceptor reflexes work normally but at a higher arterial pressure "setting." The vascular changes to pressure changes and posture, to painful stimuli, and to psychologic stresses are proportionately similar in hypotensive and normal subjects. On the other hand, fever produces a greater fall in arterial pressure in patients with essential hypertension than in normal persons. The reason for this difference is not known. It has been demonstrated in general that blood flow to the skin, brain, and splanchnic area remains the same; however, in hypertensives blood flow through the muscle is increased but diminished through the kidneys.

In the early stages of essential hypertension, the increase in peripheral resistance is due to reversible contraction of arterioles. This vasoconstriction might be due to sympathetic overaction in the presence of a circulating pressor agent or to intrinsic changes in the contractile properties of arteriolar smooth muscles.

Pheochromocytoma produces hypertension by secretion from the adrenal medullary tissue to large amounts of norepinephrine and epinephrine.

AUTONOMIC NERVOUS SYSTEM AND BIOCHEMISTRY

There is a group of hormones which cause smooth muscles to contract. Each of these, serotonin, epinephrine, norepinephrine, acetyl-

choline, and histamine, has been implicated in normal functioning of the nervous system. There are probably others still unknown.

These neurohormones are formed by specific enzymic reactions and stored away in some cellular particle, in which form they are pharmacologically inactive. On stimulation they are released to become pharmacologically active. Serotonin, for example, is stored in part in platelets of the blood.

Monamine oxidase, which is found in smooth muscles and in nerves, is an enzyme which destroys these hormones when they meet, serotonin, norepinephrine and epinephrine being monamines. Cholinesterase destroys acetylcholine in a similar fashion.

Work with monamine oxidase inhibitors arose largely from a suggestion that certain psychic abnormalities appear to arise from a deficiency of serotonin content of the brain. Now there are methods of increasing the production of the hormone apart from blocking its destruction.

Norepinephrine has been found to be active in the normal transmission of nerve impulses, and it occurs in the hypothalamus. A tranquilizing drug, reserpine, displaces this hormone from the brain, especially from the hypothalamus. Reserpine is a potent releasing agent of such endogenous monamines as serotonin, epinephrine, and norepinephrine from their binding sites; upon release, the monamines are rapidly metabolized.

In the presence of a monoamine oxidase (MOA) inhibitor, these enzymes are not metabolized. MOA inhibitors can therefore reverse the sedative action of reserpine, provided the enzyme inhibitors are given before administration of reserpine. Although the MOA inhibitors afford an increase in the brain levels of a variety of endogenous monamines, their central stimulant effects appear to be due, at least in part, to the action of dopamine. It would be helpful indeed if these interactions could be quantitated.

A well known center of integration of reflex response and control of blood pressure is located in the medulla oblongata. Direct stimulation of hypothalamic nuclei results in massive discharge of the sympathetico-adrenal system.

The sympathetic excitation for vasoconstriction is transmitted through epinephrine at peripheral synapses, although acetylcholine is necessary at the ganglionic level. The parasympathetic system has its impulses transmitted through acetylcholine, both at the ganglionic level, as well as at the neuromuscular or neuroglandular level.

The adrenal medulla is embryologically, anatomically, and functionally homologous to the sympathetic ganglia and is stimulated by acetylcholine. Furthermore, chromophobe cells are innovated by typical preganglionic fibers.

Let us now review responses of effector organs to organic nerve impulses. Adrenergic impulses (sympathetic stimulation) act on the heart at the sinoatrial node to increase heart rate; on the atria to increase contractility and conduction velocity; on the atrioventricular

node and conduction system to increase conduction velocity; on the ventricles to increase contractility, conduction velocity, automaticity, and rate of idiopathic pacemakers. All of these responses are mediated through beta receptor types.

The cholinergic response in the heart is, in the sinoatrial node, decreased heart rate (vagal effect); in the atria, decrease in contractility and increase in conduction velocity; and in the atrioventricular node, decrease in conduction velocity, atrioventricular block.

Coronary blood vessels undergo dilatation by adrenergic or cholinergic impulses. The dilatation of adrenergic impulses, however, may be due to multiple indirect causes. Skin and mucosal blood vessels have predominantly an alpha receptor and undergo constriction due to adrenergic impulses and dilatation due to cholinergic impulses. In this area, the data are uncertain. Skeletal muscle has alpha and beta receptors, and these blood vessels undergo constriction and dilatation; however, dilatation is the most common response to physiologically released circulating epinephrine. There are instances in which cholinergic stimulation causes dilatation and cholinergic response is elicited by sympathetic stimulation.

The transmitters of the nerve impulses, acetylcholine, and norepinephrine with adenosine triphosphate (ATP) are stored in the region of the axional terminals, probably within the synaptic vesicles. The calcium ion perhaps plays a part in elaborating large quantities of this for service in transmission during overstimulation. A certain quantity of these transmitters is always released during the resting state. The quantity is increased, of course, during stimulation. Acetylcholine is destroyed and dissipated by the action of cholinesterase. Whether a chemical destruction is responsible for disappearance of the adrenergic transmitter (norepinephrine) is not known. Diffusion alone may account for termination of the action of the norepinephrine, and it has been shown that diffusion accounts for disappearance of acetylcholine at some synapses.

An oversimplified chemical mechanism for the sympathetic adrenal hormones is as follows:

The amino acid tyrosine becomes dopamine. Dopamine becomes norepinephrine which can become epinephrine. These end products are classified as catecholamines, that is, dopamine, norepinephrine, and epinephrine.

In sympathetic nerves and ganglia, synthesis terminates with norepinephrine, which is stored in amounts of 5 to 10 mcg. per gram of tissue. Human adrenal glands contain much more, of course, of which 70 to 80 per cent is epinephrine and the remainder norepinephrine. The hormones are stored in intracellular granules in combination with adenosine phosphate and protein. The concentrations of free norepinephrine and epinephrine in plasma are extremely low, being less than 1 mcg. per liter.

Inactivation of catecholamines occurs through a combination of physiochemical mechanisms and metabolism by enzymes. In normal

persons, as well as those with essential hypertension, the daily urinary excretion of free catecholamines is less than 100 mcg., of which 10 to 80 mcg. is norepinephrine and 0 to 20 mcg. is epinephrine.

After adrenalectomy, excretion of epinephrine decreases, whereas that of norepinephrine shows little change. Though a potent direct vasoconstrictor, epinephrine infused in man produces generalized vasodilatation and increase in peripheral resistance, as well as striking increase in cardiac output and increase in heart rate. As a result, the systolic pressure is elevated, but the diastolic pressure remains unchanged or falls. In contrast, norepinephrine causes an increase of both systolic and diastolic pressure due to generalized vasoconstriction. Although norepinephrine is also a potent cardiotonic agent, the considerable rise in blood pressure leads to reflex slowing of the heart by the carotid sinus mechanism, and, as a consequence, cardiac output is usually unchanged. Large doses of epinephrine produce significant pressor effects, since vasodilatation secondary to accumulation of lactic acid in vascular beds, such as that of muscle, is overcome by the potent direct vasoconstrictor action of the agent.

Monamine Oxidase and Inhibitors

Monamine oxidase is one of the enzymes involved in the metabolism (and destruction) of epinephrine, norepinephrine, serotonin, tyramine, and dopamine. When iproniazide was observed to counteract the apathy and depression in mental patients, many assumed that it acts by inhibition of monamine oxidase activity in the body allowing accumulation of catecholamines. This concept can be questioned, however. Reserpine depletes the body stores of catecholamines and produces mental depression. Monamine oxidase inhibitors can block the sedative action of this drug. The low blood pressure produced by MAO inhibitors is a postural hypotension, and the exact mechanism of this action is unknown. Some of the effects resemble those seen after surgical sympathectomy. It seems paradoxical that hypotension could be due to blocking the metabolism of pressor amines. It is of interest in this connection that some patients with norepinephrine-producing tumors (pheochyromocytomas) have supine hypertension but severe postural hypotension. Hypotensive episodes also occur in patients with hyperserotonemia due to malignant carcinoid.

Nearly all norepinephrine in the body is stored in the postganglionic sympathetic fibers and disappears within a few days after section of the nerves. The small amount of residual catecholamine is largely epinephrine, which is presumably localized in chromaffin cells.

Adrenergic fibers can sustain the output of norepinephrine during prolonged periods of stimulation without exhausting their reserve supply. Reserpine causes slow release and nearly complete depletion of the entire catecholamine depots of adrenergic fibers. It reduces their uptake of injected norepinephrine for a considerable period, presumably by blocking the transport mechanism. As norepinephrine is lost, that remaining in the fiber redistributes by equilibrium causing exhaustion of both the mobile and the reserve pools.

Guanethidine produces essentially the same result but by a different mechanism. This is indicated by the observations that another antihypertensive agent, Bretylium, which prevents release of norepinephrine by adrenergic fibers in response to nerve impulses, blocks almost completely the catecholamine-depleting action of guanethidine but to a much lesser extent that of reserpine.

In addition to reserpine, drugs that inhibit the granular transport mechanism include the psychotropic agents, chlorpromazine, and imipramine, and the adrenergic blocking agent, phenoxybenzamine. Prevention by reserpine of the uptake of catecholamines by the granules with the consequent depletion of norepinephrine from the postganglionic sympathetic fibers in probably the primary basis of its action on the cardiovascular system. Nevertheless, the uptake of 5-HT is also prevented, and many of the effects of reserpine at other sites have been ascribed to this action.

Several drugs that promote release of the adrenergic mediator have already been studied. Tyramine, ephedrine, and amphetamine and related drugs cause relatively rapid, brief liberation of the transmitter and hence produce a sympathomimetic effect. On the other hand, reserpine and guanethidine bring about slow, prolonged depletion of the transmitter, which is largely metabolized as rapidly as it is released. Consequently, their sympathomimetic effects are slight, and their major effects are equivalent to adrenergic blockade.

Alpha and Beta Receptors

One of the more important factors in determining the effects of the sympathomimetic drugs is that there are two types of receptor sites with which it can react to elicit a response in sympathetic effector cells. These receptor cells differ in their physical and chemical properties in such a way as to differ in their affinity for various sympathomimetic amines. In general, the effect on alpha receptors is excitatory and that on beta receptors is inhibitory, although this is by no means an absolute rule. Certain blocking agents are selective for either alpha or beta receptors.

The smooth muscle of blood vessels supplying skeletal muscle has a preponderance of beta receptors by means of which epinephrine causes vasodilatation. It has a smaller number of alpha receptors that allows norepinephrine to constrict these vessels, since this amine has little effect on the beta receptors of smooth muscle. Isoproterenol, which acts on beta receptors and has little or no action on alpha receptors, increases the heart rate, dilates skeletal muscle vascular beds to lower blood pressure, and relaxes bronchial muscle. On the other hand, phenylephrine (Neo-synephrine), which acts on alpha receptors but has little action on beta receptors, has little cardioaccelerator action and does not relax bronchial muscle, but it raises the blood pressure by contracting cutaneous and splanchnic vascular beds. In a number of cases it is not possible, however, to predict the intensity of action of a sympathomimetic amine on any organ even though its activity on the same category of receptor in a different tissue is known. Norepinephrine, for example, elicits little

effect by means of its action on beta receptors in the smooth muscle of the bronchial tree, and in blood vessels of skeletal muscle. Nevertheless, it has considerable direct inotropic and chronotropic effects that increase the force of contraction and the rate of the denervated heart by its action on cardiac beta receptors.

Mechanism of Action of Sympathomimetic Drugs

Many sympathomimetic drugs act indirectly by releasing norepinephrine from storage site in the effector organ. Examples are amphetamine and ephedrine, which in general produce a response that is slower in onset and longer lasting than a single equipressor dose of norepinephrine. Repeated injections or continuous infusions of these indirectly acting drugs become less effective as the norepinephrine stores are diminished by continued release. Other drugs have a dual action, and act directly as does norepinephrine. Continued use of these drugs produces a response that is not abolished.

Intravenous administration of tyramine increases the amount of norepinephrine in the venous outflow of several organs *in vivo*, and at the same time reduces the organ content of norepinephrine. These effects are limited in organs pretreated with reserpine or denervated.

CATECHOLAMINES, NONCATECHOLAMINES, AUTONOMIC BLOCKING AGENTS, AND ANTIHYPERTENSIVE DRUGS

Catecholamines and Noncatecholamines

Epinephrine

Epinephrine is one of the most potent vasopressor drugs known. It can be given intravenously many times, and the response is the same, unlike ephedrine, tyramine, and other amines that owe at least part of their effect to release of norepinephrine. The effect of hypertension is produced by increased ventricular contraction, increased heart rate, and, most important, constriction of arterioles in many vascular beds especially in the cutaneous mucosa and splanchnic regions. Minute doses of epinephrine may cause hypotension, and this depressor effect is due to greater sensitivity to epinephrine of beta receptors in vascular beds dilated by the drug than of alpha receptors in vascular beds constricted by it. Therefore, subcutaneous doses of 0.5 to 1.5 mg. usually cause a widened pulse pressure, a lower diastolic pressure, an increased heart rate, cardiac output stroke volume, and left ventricular work per minute, per beat. Therapeutic doses in man increase blood flow to skeletal muscles. Arterial and venous pulmonary pressures are raised, although direct pulmonary vasoconstriction can be shown under suitable conditions. The increase in pulmonary pressure in man is predominantly, if not entirely, secondary to an increase in left atrial pressure. Overdosage may cause death by pulmonary edema precipitated by elevated pulmonary capillary filtration pressure. Coronary circulation

is enhanced by epinephrine or by cardiac sympathetic stimulation in man as well as in animals. This increase may occur without elevation in aortic blood pressure. The action on the coronary vessels themselves has been alternately reported as constrictor or dilator; however, the flow is increased. Because of the increased work, the requirement for oxygen is greater. Action of epinephrine on the heart is complicated. The cardiac arrest induced by vagal discharge from carotid sinus pressure can be abolished by an epinephrine-induced focus of impulse formation in the ventricles. The action of epinephrine in inducing cardiac automaticity and to some extent its action in causing arrhythmias are antagonized by beta blocking agents that inhibit its chronotropic and inotropic effects; however, alpha blocking agents, such as phenoxybenzamine, are strikingly effective in protecting against epinephrine-induced cardiac irregularities during induction of anesthesia with cyclopropane.

Cardiac arrhythmias have been recorded in man after accidental intravenous administration of conventional subcutaneous doses of epinephrine. Epinephrine is not indicated in shock, and the drug may accentuate the underlying disorder. Its cardiac effects may be of use in restoring cardiac rhythm in cardiac arrests due to various causes, but it is not used in cardiac failure or in hemorrhagic, traumatic, or cardiogenic shock.

Norepinephrine

Norepinephrine increases the peripheral vascular resistance in most vascular beds, and the blood flow through the kidneys, brain, liver, and usually skeletal muscle is reduced. Glomerular filtration rate is maintained unless the decrease in renal blood flow is considerable. Coronary blood flow is substantially increased, probably because of coronary dilatation and elevated blood pressure. The blood pressure effect of levarterenol, of course, is well known.

Unlike epinephrine, small doses do not cause vasodilatation or lower the blood pressure. The circulating blood volume is reduced by loss of protein-free fluid to the extracellular space, probably because of postcapillary vasoconstriction. This drug has been known to cause sinus bradycardia owing to a reflex increase in vagal tone with or without prolongation of the PR interval. Nodal rhythm, atrioventricular dissociation, bigeminal rhythm, ventricular tachycardia, and fibrillation have been observed. Respiratory minute volume is slightly increased. The drug should not be given to pregnant women, because of its contractile action on the pregnant uterus.

Phenylephrine

Phenylephrine (Neo-synephrine) is related to epinephrine, lacking in OH in the four position of the benzine ring. It is a powerful alpha receptor stimulant with little effect on the beta receptors of the heart. You will recall that the beta receptors of the heart cause an increase in heart rate, increase in contractility and conduction velocity, automatic-

ity, and rate of idiopathic pathmakers. Its action is directly on the receptors primarily, only a small part being due to its ability to release norepinephrine. Central stimulation is minimal. Systolic and diastolic pressures are raised. Effects last 20 minutes after an intravenous dose, or 50 minutes after a subcutaneous dose. There is usually reflex bradycardia, which can be blocked by atropine. Blood flow in the kidneys and skin is reduced. The circulation time is slightly prolonged, and venous pressure is slightly increased. Venous constriction is not pronounced. Phenylephine is almost completely lacking in chronotropic and inotropic actions on the heart.

Cardiac irregularities occur only rarely, even with large doses, and the reflex slowing is sufficient to permit use of the drug to end attacks of paroxysmal atrial tachycardia.

Roughly, equipressor doses are 0.8 mg. intravenously, 5 mg. subcutaneously or intramuscularly, and 250 mg. orally. Five to 10 mg. intramuscularly is the usual dosage. Use of this drug has a rational basis for relieving hypotension occurring during induction of spinal anesthesia and after sympathectomy, or from overdosage of ganglionic blocking agents, anti-adrenergic agents, or veratrum alkaloids, in temporarily constricting resistance vessels relaxed by relief from adrenergic vasoconstriction.

Amphetamine

Amphetamine raises the systolic and diastolic blood pressure. Heart rate is often reflexly slowed. With large doses cardiac arrhythmias may occur.

Noncatecholamines should not be given to patients receiving MAO inhibitors because they are destroyed by monamine oxidase, and if the monamine oxidase is inhibited, high blood pressure may be produced.

Metaraminol (Aramine)

The action of metaraminol is similar to that of norepinephrine, but it is less potent. It does not stimulate the central nervous system. Cardiac output increases strikingly when slowing of the heart is prevented by atropine. Renal and cerebral blood flow is decreased. Pulmonary blood pressure is elevated.

Methoxamine (Vasoxyl)

Methoxamine is another drug in this family which causes peripheral vasoconstriction and has little action on the heart. Sympathomimetic drugs given orally for nasal decongestion must, in general, be given in doses that do increase the blood pressure.

All of these sympathomimetic drugs are useful in shock due to spinal anesthesia. If hypotension persists in spite of administration of the drug, hypovolemia should be suspected. Also, all agents correcting hypotension cause loss of fluid from the vascular compartment. Thus, complications of pheochromocytoma leading to shock are often due to loss of circulating blood volume. Therefore, use of a sympathomimetic

drug should be considered a temporary measure only, and volume replacement the specific treatment. In general, the renal and splanchnic blood flows are already decreased in shock, and shock treated by these sympathomimetic drugs can cause further reduction in renal and splanchnic blood flow. Sympathomimetic vasoconstriction can itself produce decreased circulating blood volume. Therefore, shock that follows use of these sympathomimetic drugs usually should be combatted by careful restoration of adequate circulation and blood volume. An alpha adrenergic blocking agent may supplement fluid therapy in some of these patients by further reducing adrenergic vasoconstriction.

The shock complicating myocardial infarction differs in that reduced cardiac output is probably primary and not, as in other types of shock, secondary to inadequate venous return. Elevated blood pressure increases coronary blood flow and, presumably, the nutrition of the uninvolved myocardium, and myocardium of marginal viability; however, it also increases the myocardial work required for any given level of cardiac output, and the effect of sympathomimetic vasopressor agents on the balance between these two opposing factors has never been satisfactorily determined. Myocardial infarction predisposes to the arrhythmic action of cardio-active sympathomimetic amines.

Levarterenol, mephentermine, and metaraminol produce varying degrees of vasoconstriction and cardiac stimulation, whereas methoxamine (Vasoxyl), phenylephrine (Neo-synephrine), and the polypeptide vasopressor agent, angiotensin, have little myocardial action.

Anti-adrenergic Agents

Guanethidine

Guanethidine blocks the effect of adrenergic nerve activity. It slowly depletes tissues of catecholamines, and, at the same time, makes end-organs more responsive to catecholamines as much as one hundred fold. The most important complication of guanethidine therapy is postural hypotension, which is most pronounced shortly after the patient arises from sleep, and may be accentuated by hot weather, alcohol, or exercise. Fluid retention sometimes occurs. Ejaculation may be inhibited and associated with impotence. Guanethidine is contraindicated in patients with known or suspected pheochromocytoma because of the pronounced sensitization to circulating catecholamines that it can produce. Likewise, one might expect an over-reaction to administered catecholamines.

The Rauwolfia Alkaloids

With use of these derivatives, inhibition of the effects of peripheral adrenergic nerve activity is obviously due to depletion of norepinephrine. The once widely accepted central mechanism of suppression of the sympathetic nervous system now appears to be untenable. Reduced concentrations of catecholamines can be measured within an hour

of administration of reserpine, and depletion is maximal by 24 hours. The doses used in most laboratory experiments reduce tissue catecholamines to negligible levels. Impairment of the adrenergic nerve function usually begins at levels below 30 per cent of normal. Repeated doses have a cumulative action because *tissue catecholamines are restored slowly*. It is not clear that the usual antihypertensive doses in humans regularly reduce tissue catecholamines to levels associated with depressed adrenergic nerve function. There has been some evidence that reserpine disfavors the uptake of catecholamines by certain tissues. It does cause supersensitivity to catecholamines, just as does guanethidine. Even daily doses as small as 0.25 mg. can produce nightmares and psychic depression—sometimes severe enough to require hospitalization. Gastrointestinal motility is stimulated, diarrhea sometimes occurs, and gastric hyperacidity is present.

In common with most other antihypertensive agents, the Rauwolfia alkaloids sometimes induce sodium and water retention which can progress to frank congestive heart failure. Cardiac slowing by reserpine and digitalis can be additive. Rauwolfia therapy has been accused of producing cardiovascular lability observed particularly during anesthesia; however, studies designed to confirm this have provided negative results, and routine discontinuance of use of these agents for a period before induction of anesthesia and operation appears to be unnecessary. Congestive heart failure has been aggravated apparently by virtue of cardiac depletion of catecholamines necessary to normal contractile power.

Methyldopa (Aldomet)

Methyldopa is an effective inhibitor of dopamine. It depletes tissue stores of biogenic amines, particularly norepinephrine, including cardiac tissue. Its hypotensive action, however, is not likely related to displacement of norepinephrine from its usual site.

The role of catecholamine depletion or, indeed, of any action on catecholamine metabolism in the antihypertensive effect of methyldopa requires thorough re-evaluation. This hypothesis is questioned because: (1) Excretion of catecholamine metabolites is altered little by hypotensive doses of methyldopa. (2) Normal function of adrenergic nerves can be demonstrated even when the pressure lowering effect is minimal. (3) Other drugs deplete tissue catecholamines even more effectively than does methyldopa, but they do not lower the blood pressure of experimental animals under conditions in which methyldopa is clearly effective. The pharmacologic action is progressive reduction in blood pressure and heart rate that is maximal in four to six hours and persists for approximately 24 hours after a single dose. The fall in blood pressure is greater in hypertensives than in normotensives. It has been variously reported to be due to decreases in cardiac output, peripheral resistance, or both; postural hypotension can occur and be severe. The hypotension induced by methyldopa has not been shown to involve any major changes in distribution of blood flow. *Renal blood flow and glo-*

merular filtration are well maintained in both normotensive and hypotensive subjects, and it is considered one of the safest drugs for patients with renal disease.

Sedation is common. Vertigo and psychic depression have been reported. Retention of salt and water with development of edema and congestive heart failure may be somewhat more common with methyldopa than with most other antihypertensive agents. Other side effects are granulocytopenia, drug fever, and impairment of hepatic function. Methyldopa and its metabolites react in chemical tests for catecholamines, and their presence in blood and urine can cause false positive results of tests for pheochromocytoma. This drug has been used in patients with carcinoid disease or nonresectable pheochromocytomas.

Diuretics greatly enhance the hypotensive effects of methyldopa. Untoward reactions include dry mouth, sedation, gastrointestinal irritation, weakness, depression, headache, arthralgia, gain in weight, and acute febrile episodes with chills and aching. Alterations in results of liver function tests, including bromsulphalein, lactic dehydrogenase, and serum glutamic oxalacetic transaminase, have been observed. The drug must be given with extreme caution to patients with depressions or hepatic disease.

Other Antihypertensive Agents

Chlorothiazide (Diuril)

In addition to reducing fluid volume, chlorothiazide has an antihypertensive effect. Normotensive blood pressure is not affected, however. The stronger antihypertensive agent, diazoxide, a cousin, causes salt and water accumulation. Available evidence indicates that the major antihypertensive effect of the thiazides is due to direct relaxation of the smooth muscle of resistance vessels, namely arterioles. The mechanism of this effect is not clear. Absence of a significant effect on capacitance vessels allows adequate venous return even in the presence of the gravitational stress of an erect posture, and, therefore, venous pooling and postural hypotension do not occur. By reducing blood volume, however, the thiazides often cause postural hypotension when given with other antihypertensive agents. Norepinephrine, but not angiotensin, affects these capacitance vessels.

Monamine Oxidase Inhibitors

Of the monamine oxidase inhibitors, pargyline (Eutonyl) remains most popular. It is used also as an antidepressant. It has been suggested, on the basis of indirect evidence, that inhibition of MAO might inhibit transmission in ganglia by allowing local accumulation of norepinephrine. The effect of MAO inhibitors is postural hypotension without associated tachycardia. Hepatocellular degeneration, blood dyscrasias, and optic atrophy have been reported. A MAO inhibitor and methyldopa should not be combined in antihypertensive therapy, because this com-

bination can produce severe central nervous system stimulation and a hypertensive reaction under certain circumstances. Pargyline promotes fluid retention and nonfluid gain in weight, both of which present problems in medical management. Insomnia, nightmares, psychotic reactions, muscle cramps, and other reactions have been reported. With other drugs and unsuspected constituents of diet, extremely severe hypertensive and hyperthermic crises can develop. Cheddar cheese and drugs such as amphetamines have caused hypertensive crises. Demerol may induce *hypotensive* crises. Hyperthermic crises may occur when imipramine hydrochloride (Tofranil) is used.

Veratrum Alkaloids

Veratrum is mentioned to exemplify the effects of the ester alkaloids which have been studied in connection with hypertension and hypotensive effects. The cardiovascular and respiratory systems are profoundly affected by low doses of the active alkaloid. The major cardiovascular effects are reflexive. The terminations of central afferent fibers from pressor or stretch-sensitive areas of the circulatory system are susceptible, and, in the presence of the ester alkaloid, initiate more impulses at any given level of stimulation than under normal conditions. This higher impulse traffic in afferent fibers is interpreted by coordinating areas in the brain stem as denoting a pressure higher than that actually present. As a result, the negative feedback mechanism that normally subserves blood pressure homeostasis is activated, sympathetic tone is decreased, vagal tone is increased, and the pressure is thereby reduced. Blood pressure is decreased, and the heart is moderately slowed. Atropine abolishes the bradycardia but only partially reverses the hypotension.

Because the compensatory mechanisms are reset rather than blocked, the fall in blood pressure does not have a major postural component, cardiac output is only moderately decreased, and cardiovascular reflexes, such as those induced by cold pressor tests of Valsalva's maneuver, are not blocked. Total peripheral resistance is decreased; circulation blood flow to the limbs, kidneys, and liver is slow initially and then becomes almost normal, although the hypotension persists. Venous distensibility is increased. Antidiuresis occurs initially but tends to disappear if the hypotension is prolonged. The action apparently is due to release of the antidiuretic hormone.

Large intravenous doses may cause transient cardiac arrhythmias, heart block, and ventricular premature contractions, most of which are accentuated by administration of digitalis and abolished by use of atropine. The margin between the therapeutic and toxic doses is narrow, and this margin is even narrower when continued medication is required. Nausea and vomiting are major complications. Substernal burning, unpleasant taste, salivation, sweating, and hiccough are common. Blurring of vision and mental confusion may appear. Cardiac arrhythmias are more likely to occur in patients receiving digitalis. These arrhythmias are relieved sometimes by administration of atropine. Veratrum is indicated chiefly in patients whose treatment is to be of

limited duration and in certain hypertensive emergency conditions, particularly toxemias of pregnancy.

Hydralazine

Hydralazine (Apresoline) reduces the diastolic pressure. The heart rate, stroke volume, and cardiac output are increased. Splanchnic, coronary, cerebral, and renal blood flows are increased unless the blood pressure drops precipitously. Sometimes sodium retention occurs. The general hemodynamic state produced by hydralazine may accentuate specific inadequacies; for example, hydralazine may considerably increase the pulmonary artery pressure in patients with mitral valve disease. Large doses may reduce the pressor response to epinephrine and impair ganglionic transmission. The exact mode of action is not understood. Continued administration in doses greater than 400 mg. a day has produced an acute rheumatoid state indistinguishable from disseminated lupus erythematosus in a small percentage of patients.

Autonomic Blocking Agents

Sympathectomy

Sympathectomy produces predominant orthostatic reduction in blood pressure which may be temporarily disabling, while recumbent pressure is little affected. Side effects are postural hypotension, neuritic pain, patchy sweating in undenervated areas, impaired ejaculation in the male, and nasal congestion.

Hexamethonium

The effects of ganglionic blockade cause vasodilatation of the arterioles with increased peripheral flow and hypotension, pooling of blood, decreased venous return, decreased cardiac output, tachycardia, reduced tone and motility of the gastrointestinal tract, constipation, urinary retention, dry mouth, and anhidrosis. The importance of existing sympathetic tone in determining the degree to which blood pressure is lowered by ganglionic blockade is illustrated by the fact that blood pressure may be decreased only minimally in recumbent normotensive subjects but may fall sharply in sitting or standing subjects. Postural hypotension is common. The cold pressor response is reduced. These blocking agents reduce blood pressure even in patients who have undergone sympathectomy, because ganglionic vasoconstrictive pathways are sometimes not removed surgically. Blood pressure is further reduced by sympathectomy, sodium depletion, and administration of hydralazine.

Usually, mild tachycardia accompanies the induced hypotension. Cardiac output often is reduced; however, in patients with cardiac failure, these blocking agents frequently cause increased cardiac output because of reduction in peripheral resistance and decreased pressure in the right side of the heart resulting from decrease in venous return. A direct positive inotropic effect of hexamethonium on the myocardium

has been demonstrated and may contribute to the increased cardiac output of the decompensated heart. In ganglionic blockade, the skin receives more blood. Skeletal blood flow is unaltered, and splanchnic blood flow is usually decreased. There is usually a reduction in cerebral blood flow. However, in hypertensive patients with retinopathy, hexamethonium has been shown to reduce equally cerebral vascular resistance and mean arterial pressure without producing a significant alteration in cerebral blood flow, changes that are favorable for cerebral hemodynamics in hypertension. It reduces coronary vascular resistance and has variable effects on coronary blood flow in hypertensive patients.

In normal subjects, hexamethonium reduces glomerular filtration and renal blood flow; however, in some hypertensive patients, this reduction does not occur. In patients with malignant hypertension, continued use of hexamethonium may cause progressive renal insufficiency and uremia, terminating in death. Gastric secretions are decreased. Achlorhydria may be produced. Pancreatic secretions are reduced. Biliary secretions are reported to be either unaffected or slightly enhanced. Diminished salivary secretion is another consequence of ganglionic blockade. Constipation has already been mentioned.

The more severe reactions include pronounced hypotension, constipation, paralytic ileus, and urinary retention. Angina may be precipitated. Syncope may occur without warning. The effects of hexamethonium are enhanced when hydralazine is used concurrently. During hexamethonium therapy in a severely hypertensive patient, unexpected pulmonary dyspnea associated with radiologic changes in the lungs may occur and death may ensue. The pulmonary lesion, organized fibrinous edema, is thought to be due to attacks of left heart failure modified by intermittent hypotension. Fatalities from uremia have been reported in patients with malignant hypertension. Therefore, caution must be exercised in the use of ganglionic blocking drugs in patients with cerebrovascular, coronary, cardiac, or renal insufficiency. Gastric retention of food and secretions is sometimes hazardous. Since the catecholamine action is enhanced by ganglionic blockade, the conventional doses for a patient receiving hexamethonium should be reduced accordingly. Intestinal absorption of hexamethonium is unpredictable. Elimination is chiefly through the kidneys. Dosage must be highly individualized, and the patient must be closely supervised. Other agents in this group include mecamylamine (Inversine); pentolinium tartrate (Ansolysen); and trimethaphan (Arfonad).

Parasympathetic Block

Prominent side effects of parasympathetic ganglion blocking agents are common and potentially serious, principally paralysis of the bladder and intestines.

Atropine

Average clinical doses of atropine are 0.4 to 0.6 mg. (150 to 300 gr.); larger doses cause progressively increasing tachycardia by blocking

vagal effects on the sinoatrial pacemaker. Maximal heart rate (response to exercise), however, is unaltered by use of atropine. The influence of atropine is most noticeable in healthy young adults, in whom vagal tone is at its height. In infancy and old age, even large doses of atropine may fail to accelerate the heart rate. Atropine blocks the heart-slowing action of carotid sinus stimulation, pressure on the eyeballs, and the normal afferent impulses causing respiratory arrhythmia; it abolishes bradycardia or asystole from injection of cholinesters, anticholinesterase agents, or other parasympathomimetic drugs. Atropine given as 1.2 mg., subcutaneously, has a constant effect on the electrocardiogram in human beings in significantly lowering the T waves usually in all three limb leads. Atropine will correct the shock which is produced by peripheral dilatation caused by cholinesters; however, it has little effect on the blood pressure when given alone. It is a specific drug for the shock due to improper use of cholinesters, such as acetylcholine and methacholine. Methacholine has been used in the treatment of paroxysmal atrial tachycardia, because it acts as a vagomimetic drug; however, atropine is sometimes necessary to counteract the shocklike condition which it produces.

Adrenergic Blocking Agents

Adrenergic blocking agents inhibit responses to adrenergic sympathetic nerve activity and to epinephrine and other sympathomimetic amines. The locus of action is the effector cell, which distinguishes such agents from substances that prevent sympatho-adrenal discharge by blocking nerve impulse transmission within the cerebrospinal axis, in autonomic ganglia, or along peripheral neurons, or that interfere with release of adrenergic mediator-like norepinephrine. Alpha receptors produce increased blood pressure to norepinephrine; beta receptors respond to isoproterenol.

Before 1958, all known adrenergic blocking agents affected mainly the alpha adrenergic receptors and were unable to prevent myocardial stimulation, bronchial smooth muscle relaxation, and vasodilatation of the skeletal muscle, which are beta receptor functions. The blocking agents are almost entirely specific for one or another of these functions. These alpha adrenergic blocking agents have little effect on the blood pressure of normotensive subjects unless they are hypovolemic. In hypertensive subjects, they produce orthostatic hypotension.

One drug in this series, phenoxybenzamine (Dibenzyline), has been used to treat patients with Raynaud's disease, acrocyanosis, causalgia, and chronic ulceration of the limbs. The ergot alkaloids were the first adrenergic blocking agents to be discovered; however, they have important pharmacologic properties concerning direct stimulation of the smooth muscle, and complex excitation and depression of the central nervous system.

Phentolamine produces a moderately effective, competitive alpha adrenergic blockade that is relatively transient. Five milligrams of phentolamine effectively reduces the blood pressure if it is elevated by

action of pheochromocytoma. False positive and false negative responses are more common in patients who are azotemic or receiving sedatives or narcotics. Tachycardia and dizziness usually develop. The drug has been used in treatment of shock to counteract vasoconstriction.

Protection can be attributed to three specific antishock effects: (1) increased total blood flow, particularly in the abdominal viscera; (2) local redistribution of blood flow so that a larger percentage passes through channels that readily exchange metabolites with tissue cells, presumably true capillaries, and (3) reversal of the vasoconstriction-induced shift of fluid from the vascular to the interstitial compartment. Thus, phenoxybenzamine is under investigation for treatment of patients in shock; results have been encouraging.

In addition to its specific antishock effects seen sometimes in patients operated on for pheochromocytoma, two other effects of phenoxybenzamine might contribute to the practical clinical management of certain conditions in the future:

1. The fall in blood pressure induced only when it is administered to hypovolemic patients provides a quick and reliable indication of the inadequacy of intravascular fluid volume replacement, a point often difficult to assess.

2. The shift of blood from the pulmonary to the systemic vascular bed associated with blockade of sympathetic vasomotor tone allows administration of larger volumes of fluid more rapidly than would otherwise be possible, particularly with patients with some myocardial inadequacy.

Isoproterenol

Isoproterenol has a powerful action on beta receptors and almost no action on alpha receptors. Its main actions are therefore on the heart, smooth muscle of the bronchi, skeletal muscle vasculature, and alimentary tract. On the cardiovascular system it lowers the peripheral vascular resistance mainly in skeletal muscle but also in renal and mesenteric vascular beds, and the diastolic pressure falls.

AN IMPORTANT PRESSOR AGENT

Angiotensin

Angiotensin is physiologically produced when the enzyme, renin, liberated from storage sites in the kidney, acts on the substrate angiotensionogen, a plasma globulin. The first product is angiotensin I, which is pharmacologically inert; however, through the action of a further enzyme system present in the plasma and many tissues, it is rapidly converted to the active octapeptide, angiotensin II. Angiotensin produces intense vasoconstrictor and pressor reactions. It is a powerful stimulant to the secretion of aldosterone. The blood pressure is increased as a direct stimulant action on vascular smooth muscle. The precapillary region is most affected. Postcapillary vessels and veins are only

feebly constricted. The effect is strongest in the vessels of the skin, splanchnic region, and kidney, and the blood flow in these organs falls sharply. The effect is less in the vessels of skeletal muscle and in cerebral and coronary vessels, and blood flow in these beds is maintained or increased as the relatively weak vasoconstrictor response is opposed by the elevated systemic blood pressure.

In vivo, positive inotropic effects are inconstant and fleeting, and there is no sustained increase in myocardial contractility. Usually, the heart rate is slowed by reflex action. Cardiac output may fall slightly. There is an increase in the work done by the heart, but this is usually unaccompaned by evidence of coronary insufficiency, presumably because the raised systemic blood pressure insures an adequate coronary blood supply despite the coronary constrictor action of angiotensin.

For blood pressure angiotensin is the most powerful stimulant known, molecule for molecule. It is about forty times as active as norepinephrine. Systemic blood pressure in man has been raised by infusing as little as 0.002 micrograms per kilogram of body weight each minute. The response occurs in one minute, and blood pressure returns to normal in about five minutes. It is less likely to be followed by hypotension. It has little or no tendency to set up disturbing arrhythmias. It can be combined with anesthetics, such as cyclopropane and other halogenated hydrocarbon agents. There is no tissue necrosis or sloughing; however, it shares the disadvantage that it diminishes blood volume by promoting loss of protein-free fluid from the circulation to tissue spaces. It does not reduce the venous reservoir as effectively as does norepinenphrine.

SUMMARY

The common clinical course of essential hypertension is fairly well known, but the cause and results of treatment are not fully appreciated even in the light of an abundant new body of information regarding the etiologic influence of the autonomic nervous system, and on the mechanism of drug action. It is, therefore, not practical to discuss unusual "laboratory" manifestations of essential hypertension.

Essential hypertension is unusual when it mimics hypertension which has a cause. Likewise, these diseases masking as essential hypertension may be considered under "unusual manifestations." Many "unusual manifestations" occur clinically during treatment of hypertension with old and new agents. These range from interesting nuisances to life-threatening reactions. Many such reactions are unavoidable, justifiable, and sometimes *necessary*. Some are absolutely unnecessary and inexcusable. This is true when powerful agents whose total action is not appreciated, are used to treat a sign only and not specifically to correct a pathophysiologic process. Herein is presented information which must bear on intelligent recognition, appreciation, and management of unusual manifestations of essential hypertension. This information has been gathered from standard reference sources and arranged in an attempt to fit the practitioner's needs.

Acute Renal Failure: Its Unusual Causes and Manifestations

JULIO E. FIGUEROA, M.D.

Acute renal failure may be defined as relatively sudden, rapidly progressive loss of renal function, resulting in the uremic state with all its clinical and biochemical manifestations. Oliguria (urinary volume less than 400 ml./24 hr.) usually accompanies this clinical entity, although the urinary volume may be normal;[15] at times, even polyuria has been associated with the initial phase of acute renal failure.[5]

The most common causes of acute renal failure are conditions associated with greatly reduced blood volume, hypotension, and nephrotoxic substances, such as mercury, carbon tetrachloride, and ethylene glycol.[10, 11] About 75 per cent of cases of acute renal failure are associated with blood transfusion reactions, obstetrical accidents such as septic abortion and postpartum hemorrhage, and trauma or surgical procedures, particularly aortic or open heart surgical procedures.[13, 14, 17] In children, nephrotoxic substances are second only to acute glomerulonephritis as a single cause of acute renal failure.[2] The histopathologic changes in acute renal failure depend on the cause of the clinical syndrome.[19, 30] Acute tubular necrosis is the most common underlying abnormality. Occasionally, no light microscopic abnormality can be found in patients with acute renal failure.

UNUSUAL CAUSES

Renal Arterial and Venous Occlusion. Bilateral thrombosis of the renal artery is a rare cause of acute renal failure. Occlusion of the renal veins is slightly more common. In both conditions, pain in the flank, gross hematuria, severe oliguria, and at times anuria are the rule. There is transient elevation of the serum glutamic oxalacetic transaminase level. In renal vein thrombosis, the engorged kidney can be felt as an abdominal mass. Complete occlusion of the renal veins is more

From the Department of Internal Medicine, Ochsner Clinic, New Orleans, Louisiana

common in children than in adults and is associated with shock. Partial occlusion may be accompanied by oliguria, and the nephrotic syndrome may develop immediately after occlusion of the vein. Renal vein thrombosis is associated with a high incidence of pulmonary emboli; acute renal failure with pain in the flank and signs of pulmonary emboli should make one suspect this condition.[24]

An extremely unusual cause of acute renal failure, associated with impairment of renal venous return, is an expanding intrahepatic hematoma producing compression of the intrahepatic portions of the inferior vena cava.[32] Surgical release of the pressure on the inferior vena cava results in complete recovery.

BILATERAL CORTICAL NECROSIS. Bilateral cortical necrosis is an uncommon cause of acute renal failure. Its association with a variety of clinical conditions, including criminal abortion and drug hypersensitivity, has been reported. The patient with this condition is desperately ill and extremely toxic. Leukocytosis, fever, and shock may persist in spite of adequate therapy. Urinary excretion is characteristically low, and anuria (urinary volume of less than 200 ml./24 hr.) is common. Most patients do not have diuresis and die from renal insufficiency.[33] For this reason, the patient with acute renal failure who has not undergone diuresis within the usual period of 7 to 14 days after the initial insult should be suspected of having cortical necrosis. Renal biopsy helps to indicate further therapeutic approach.

ACUTE GLOMERULONEPHRITIS IN ADULTS. Although acute glomerulonephritis is the most common single cause of acute renal failure in children,[2] it is a rare cause in adults. A history of streptococcal sore throat, followed by the usual delay before symptoms of acute glomerulonephritis develop, should suggest this diagnosis. Oliguria can be prolonged, and the symptoms of uremia are usually severe.[23] Recently, use of high doses of corticosteroids, together with dialysis, has resulted in diuresis with partial or complete recovery in a significant percentage of patients.[23]

"AUTOIMMUNE" DISEASES. Rapidly progressive renal failure associated with severe pulmonary disturbances has been described in patients with such unusual conditions as polyarteritis nodosa and its variant, Wegener's granulomatosis, as well as Goodpasture's syndrome.[24] In the first two conditions, acute renal failure may be present with or without oliguria. Prominent systemic manifestations, and in particular evidence of vasculitis and pulmonary failure, as well as eosinophilia, are characteristic of these conditions. In Wegener's granulomatosis, the mucous membranes of the nose and sinuses are usually involved and serve as a differential point. In both conditions, the chances of recovery after uremia develops are slim, and the response to corticosteroid therapy is unpredictable. In Goodpasture's syndrome, recurrent hemoptysis, associated with microcytic anemia, usually appears before signs of renal failure. Once renal failure is established, death typically occurs within a few weeks to a few months. The response to corticosteroids is poor.

MALIGNANT RETICULOENDOTHELIAL DISEASES. Acute renal failure is an unusual manifestation of the lymphoproliferative disorders. Mild, chronic elevations of urea nitrogen are more frequent. The mechanisms for development of acute renal failure are of three different types: (1) obstructive uropathy secondary to bilateral ureteric blockade, either by lymph nodes in the retroperitoneum or by retroperitoneal fibrosis, (2) acute hyperuricemia precipitated by use of cytotoxic agents in an effort to control the lymphatic disease, and (3) diffuse infiltration of the kidneys by malignant cells.[1, 3] In obstructive uropathy, total anuria of sudden onset is characteristic, whereas in the other two anuria is uncommon. Severe hyperuricemia is characteristic of the second type and, when malignant cells infiltrate the kidneys, these organs may be palpable. The response of the obstructive uropathy and the malignant infiltration in the lymphomatous diseases to radiation therapy is variable, but transient relief of acute renal failure has been reported with such therapy.[3] In hyperuricemia associated with treatment for these diseases, use of large quantities of fluid and alkalinizing agents has been advocated to prevent development of acute renal failure. With the recent advent of drugs which block the synthesis of uric acid, such as allopurinol, it should be possible to prevent, or at least minimize, the hyperuricemia associated with these diseases.

Multiple myelomatosis can produce acute and chronic renal failure by several mechanisms.[26] The chronic renal failure of the myelomatous kidney is usually due to amyloid disease or to spillage of large amounts of myelomatous proteins in the urine. Acute renal failure, on the other hand, can be precipitated in these patients by acute, severe dehydration with precipitation of the Bence-Jones protein and the myelomatous proteins acutely in the tubules.[21] It can also occur with the hypercalcemia associated with multiple myelomatosis. Oliguria with rising azotemia in patients with myeloma has been found to be associated with intravenous urography. At first the contrast medium was thought to cause the acute renal failure, but more recently it has been recognized that renal failure is due to the concomitant dehydration in preparation for the radiologic study.[21] When oliguria and hypercalcemia with rising azotemia occur in the patient with multiple myelomatosis, rapid hydration and corticosteroid therapy have been successful in restoring the urine volume and normalizing the serum calcium without producing acute renal failure.[25]

MYOGLOBULINURIA, HEMOGLOBULINURIA, AND THE HEMOLYTIC UREMIC SYNDROME. Acute renal failure associated with red urine that does not contain red blood cells is usually the result of myoglobulinuria or hemoglobulinuria. Myoglobulinuria occurs most commonly in the acute renal failure associated with crush injuries and high voltage electric shock. Rarely, acute renal failure has been reported in patients with idiopathic myoglobulinuria.[31] Hemoglobulinuric acute renal failure occurs commonly in patients with burns and hemolytic transfusion reactions. Rarely, paroxysmal cold hemoglobulinuria associated with syphilis may cause acute renal failure.[20]

The hemolytic uremic syndrome is a rare disease characterized by acute renal failure, associated with profound hemolytic anemia with bilirubinemia and severe thrombocytopenia. Hematuria and anuria are common. Proteinuria and cylindruria are usually severe. Neurologic manifestations are prominent and include lethargy, convulsions, and paresis. The syndrome occurs characteristically in infants and children, most being younger than 12 months of age. Diarrhea precedes the acute renal failure by some time. Usually, it subsides and acute hemolytic anemia and associated renal failure then develop. The red blood cells have a characteristic triangular shape, and fragmentation of erythrocytes is common. These cells are different from the "burr" cells, which are characteristic of uremia. In the hemolytic uremic syndrome, the pathologic changes are variable and such pathologic alterations as renal cortical necrosis, vasculitis with hyaline thrombi, and acute glomerulonephritis have been described.[22]

MISCELLANEOUS CAUSES. Acute renal failure after electroshock therapy is rare. The reason for its occurrence is not clear, and physiologic studies in animals receiving electroshock have uncovered no constant abnormalities in renal function.[28]

Diabetic acidosis rarely produces acute renal failure. When it does, the diagnosis may not be recognized because the acidosis can be explained on the basis of ketone bodies, and oliguria may not develop owing to the osmotic diuresis. Acute pancreatitis has been associated with uremia and, in particular, acute hemorrhagic pancreatitis and acute renal failure have occurred concomitantly, sometimes in the absence of shock or other stimuli to the production of renal failure.[12] Acute renal failure has been said to occur in 10 per cent of patients with cholera. The clinical course is typical of acute tubular necrosis with oliguria and rising azotemia, but the pathologic changes show pronounced vacuolization of tubular cells, compatible with a diagnosis of hypokalemic nephropathy. These patients lose large quantities of potassium through the stools, and hypokalemia may develop in spite of acute renal failure.[6]

UNUSUAL MANIFESTATIONS

Manifestations Due to Uremia

Neurologic manifestations of the uremic syndrome have been long recognized.[16] The neuromuscular manifestations, however, have been overlooked for many years because more life-threatening manifestations of the disease attracted the attention of investigators. Since dialysis has become common treatment for uremia, the neuromuscular manifestations of this syndrome have become more important.

Uremic polyneuropathy may be characterized by sensory or motor manifestations. Paresthesias, decreased vibratory sensations, and hyperesthesias have been reported.[16] Motor neuropathy can be striking, particularly in patients with chronic uremia. It is usually more prominent in the lower limbs, but it may affect the upper limbs as well. More severe disease may cause complete quadriplegia.

Myoclonus (jerky movements and twitching of muscles) and convulsions are common manifestations of the uremic syndrome. Acute sustained muscular spasm in uremia, however, is a rare symptom of acute renal failure. It closely resembles the acute sustained tetanic contractions seen in patients with Clostridium tetani infection.[9] The myospasm of acute renal failure has not been correlated with abnormalities in serum calcium, serum magnesium, or acidosis.

The psychiatric manifestations of uremia range from forgetfulness to acute toxic psychosis with hallucinations. These manifestations, as well as the neuromuscular symptoms, are relieved by efficient dialysis.

Occasionally, a patient with uremia is referred to a hospital because of acute bleeding from the gastrointestinal tract or from other sites. Bleeding tendencies are common in acute renal failure, but acute gastrointestinal bleeding with hematemesis or melena is not as common. When it occurs in a patient with acute renal insufficiency, a diagnosis of acute mercury poisoning should be considered. The gastrointestinal manifestations of acute mercury poisoning may predominate over the uremic symptoms and in many patients are the cause of death.[27]

In patients with acute renal failure who do not have primary pulmonary disease, expiratory wheezing, elevated venous pressure, and right ventricular electrocardiographic abnormalities suggestive of cor pulmonale may occur. These manifestations may resemble those of pulmonary emboli, but no evidence of pulmonary infarction has been found at necropsy of many of these patients.[24] The uremic, hemorrhagic alveolitis may be responsible for these clinical manifestations.

Since total anuria rarely occurs in acute renal failure secondary to acute tubular necrosis, other conditions, such as obstructive uropathy, vascular occlusion, and cortical necrosis, should be suspected. On the other hand, a normal or large urinary volume may occasionally occur in the presence of rising azotemia in such cases as diabetic acidosis.

The electrocardiographic changes of acute uremia are usually the manifestations of electrolyte imbalance, namely hyperkalemia and hypocalcemia. The usual T-wave elevation, disappearance of the P wave, and widening of the QRS complex are well known manifestations of hyperkalemia. Occasionally, however, abnormally wide and deep Q waves and ST segment elevation may occur in patients with acute uremia, reversed and by correction of hyperkalemia and probably secondary to it. These changes may simulate myocardial ischemia, as well as myocardial injury.[7]

In patients with acute renal failure secondary to acute tubular necrosis, the urinary findings are characterized by a low urea concentration with a ratio of urinary urea to blood urea concentration of as low as 5 and a high sodium concentration.[10, 11] The osmolality of urine as a rule is low in the early stages of acute renal failure due to tubular necrosis. These laboratory data help differentiate oliguria secondary to prerenal factors without parenchymal renal damage from acute tubular necrosis in most cases. In acute glomerulonephritis with oliguria and in acute renal failure secondary to burns, however, the urinary urea concentration may be high with a high specific gravity of urine, and the

urinary sodium concentration may be low, that is, lower than 40 mEq./24 hr.[10, 11] Rarely, this situation can be seen in post-traumatic or post-hemolytic acute renal failure. With the introduction of osmotic diuresis in test doses to differentiate between prerenal oliguria and acute renal failure,[4] elevated specific gravities due to mannitol are occasionally seen in patients with acute tubular necrosis.

Manifestations Due to the Primary Cause of Acute Renal Failure

Severe hypercalcemia with all its clinical manifestations can mask and mimic the manifestations of acute renal failure in patients with multiple myelomatosis, sarcoid, or hyperparathyroidism.[25] In these patients acute psychotic episodes and coma may develop with mildly elevated levels of blood urea nitrogen and may revert to normal after correction of the hypercalcemia.

Muscle necrosis and calcification have been reported in acute renal failure secondary to barbiturate intoxication.[8] The exact cause for the muscle necrosis and the calcification is not known, but pressure on the affected muscles from positioning of the body after long periods of coma, has been incriminated. In idiopathic myoglobulinuria, pronounced muscle weakness can be a major symptom, and death from respiratory failure may occur. The pulmonary-renal syndromes seen in the connective tissue diseases, as well as Goodpasture's syndrome, have been described already.

The hepatorenal syndromes can be divided into two components. The first is progressive renal failure in patients with mild hepatitis, Weil's disease, and others. In the second, the acute renal failure that sometimes occurs in patients undergoing operations on the gallbladder, as well as in the cirrhotic patient, has been thought to be related to the hepatic disease.[29] In these patients the manifestations of hepatic disease may be severe, and jaundice and ascites may initially mask the manifestations of acute renal failure. In patients with leptospirosis, characteristically, the acute febrile illness with jaundice and systemic manifestations precedes development of oliguria and acute renal failure. The pathologic alterations in this large group of conditions range from none to glomerular base membrane thickening.[29]

Finally, recurrent acute renal failure has been reported as a medical curiosity.[18] Occurrence of a second episode of acute renal failure during the diuretic phase or the first episode of acute renal failure is extremely rare. The second episode is usually due to a new precipitating cause occurring during the diuretic phase of the first episode. In the two cases reported,[18] recovery followed the second episode of acute renal failure. One of the patients regained normal renal function and the other partial function.

CONCLUSIONS

Of utmost importance to the physician is the prevention of acute renal failure. Once prevention is no longer possible, early recognition of

the manifestations of acute renal failure is equally important, since a large number of lives may be saved by early institution of adequate therapy.

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Evidence of Hepatic Disease That May Be Overlooked

W. D. DAVIS, JR., M.D.*

Whereas most of the frequent clinical and laboratory manifestations of common hepatic diseases are well known, a number of less usual but often diagnostically significant manifestations are not widely appreciated. In our experience, some of these have provided the clue to early correct diagnosis. The catalogue here presented is far from complete but might be of help to physicians who are consulted by patients with symptoms referable to the liver.

HEPATITIS

In patients with acute infectious hepatitis, the influenza-like onset, general malaise, lassitude, anorexia, loss of taste for cigarettes, abdominal or right upper abdominal quadrant discomfort, dark urine, tender liver, ultimate jaundice, and the florid laboratory evidences of parenchymal hepatic cellular damage are commonly known. But how many of us remember that the presence of a small lymph node (2 or 3 mm. in diameter) at the level of the right seventh cervical transverse process may be of considerable help in suggesting a diagnosis of acute viral hepatitis instead of mechanical obstruction? Likewise, we need remember that homologous serum jaundice, in contradistinction to the usual acute infectious hepatitis, may be insidious in onset, presenting well developed jaundice without the slightest warning or with the mildest prodromal lassitude of several weeks' duration. The clinical course may be prolonged—up to 12 months—with recovery, but chronic or continuing disability sometimes results. Conversely, the onset of acute infectious hepatitis may be so fulminant in rare instances that delirium, mania, coma, and death may occur within the first few days even before icterus has become clinically apparent. Salt and water retention is invariably present in the developing and active phases of acute hepatitis, and when sought for, demonstrable edema and on rare occasions extensive ascites may be found. One of the early and most encouraging signs

From the Section on Gastroenterology, Ochsner Clinic, New Orleans, Louisiana

of convalescence is the beginning of spontaneous diuresis in this condition.

From the laboratory standpoint, in uncomplicated acute infectious hepatitis, we are perhaps not likely to remember that the erythrocyte sedimentation rate is always normal, and neutrophilic leukopenia with relative lymphocytosis is almost invariably present. Likewise, at the height of activity of the disease, even in the presence of jaundice, retention of bromsulphalein is predictably higher than 50 per cent, a finding which may be of help in differentiating this condition from mechanical obstructive jaundice. Finally, from the standpoint of management of acute infectious hepatitis, except in the instance in which inclusion of fat in the diet adds to nausea and anorexia, no useful purpose is served by limiting fat in the diet, whereas addition of sufficient fat to make the diet palatable is likely to enable the patient to eat more, with therapeutic benefit.

The question of the value of corticosteroids in the treatment of complicated or chronic hepatitis is as yet unsettled. Our experience includes, as noted, instances of prolonged hepatitis with complete recovery without benefit of corticoids, and apparently dramatic benefit from the administration of prednisone or similar drugs followed by easy withdrawal and apparent complete recovery. There are also patients who have obtained no benefit and whose disease has been steadily progressive and finally fatal, despite huge doses of corticosteroids. Finally, some patients apparently have become dependent on steroids, that is, after prolonged periods of suppression with prednisone, they will have relapses upon its withdrawal, requiring resumption of its use. In these patients, in our experience as well as that of others, despite improvement in the results of liver function tests serial biopsies of the liver show no change. In a single tragic instance of a patient who had prolonged corticoid treatment, death was due to compression of the cervical cord related to collapse of osteoporotic cervical vertebrae resulting from prolonged corticoid treatment.

PAIN

Whereas the dull pain of hepatitis and the severe waves of true biliary colic are commonly recognized, it should be remembered that in hemochromatosis particularly, and in the Dubin-Johnson variety of idiopathic hyperbilirubinemia, episodes of pain may occur in the right upper abdominal quadrant of such severity as to be mistaken for biliary colic and lead the unwary physician to operate. About 50 per cent of patients with hemochromatosis and perhaps 30 per cent of those with Dubin-Johnson syndrome have such pain. In those with hemochromatosis, multiple phlebotomies result in relief of these pains as the other manifestations of the disease improve.

In patients with hemochromatosis, sometimes laboratory evidence of hepatic damage is much less impressive than are the clinical signs. For example, bromsulphalein retention of 0, 10, or 15 per cent is usually

the rule, or proteins may be normal in the face of obvious evidence of rather severe clinical difficulty.

An example is the case of a 53-year-old woman seen in 1959 with a history for two years of attacks of severe pain in the right upper abdominal quadrant and right flank extending to the back. Initially, the pain was steady and worse on inspiration but became increasingly severe during a period of 24 hours and lasted approximately one week at a time. Attacks might occur every two or three months. A fat-restricted diet resulted in apparent relief for six months. Gallstones were suspected, and with recurrence of pain in August, 1958, cholecystectomy was performed in another hospital. No stones were found, but the liver was hard and nodular. On microscopic section the histologic appearance was typical of hemochromatosis.

On examination the liver was palpated 6 to 7 cm. below the right costal margin, and the spleen could not be felt. The skin was a dusky, brownish-blue with changes most pronounced over the exposed areas and shins. Telangiectasia was noted over the shoulders and arms, some of which were true spider nevi. Ecchymoses were noted on the skin over the backs of the hands. Bromsulphalein retention was only 8 per cent at the end of 45 minutes; the serum iron content was 157 mg./100 ml., 100 per cent saturated. Serial phlebotomies were accomplished during the ensuing months with maintenance of the hemoglobin levels between 10 and 12 gm. in contradistinction to the previous level of 14.5 gm. Within three months after the first phlebotomy at the rate of 1 pint weekly, the pain in the right upper abdominal quadrant became less severe, and after about nine months it disappeared not to return, except on one occasion about two years after institution of treatment, when the phlebotomies had been discontinued and the hemoglobin value was normal. The patient was again asymptomatic one year later: the hemoglobin was about 10 gm., hematocrit 35 per cent, and serum iron content 70 mcg./100 ml. In 1966 the patient was well and had no further pain.

FEVER AND LEUKOCYTOSIS

Fever, often with chill and severe neutrophilic leukocytosis, is frequently recognized as evidence of common duct obstruction with ascending cholangitis. We are likely to forget, however, that these are also manifestations of acute exacerbation of alcoholic disease of the liver, which is associated with severe fatty infiltration of the liver, hepatocellular necrosis, and neutrophilic infiltration of the hepatic lobule; we prefer to call this acute alcoholic hepatosis, though it is perhaps more commonly known as acute alcoholic hepatitis. Daily temperature of 104° F. may persist, and for weeks neutrophilic counts of 25,000/cu.mm. or more are common. Recognition of this syndrome is important because of its high mortality rate (up to 50 per cent) and a tendency for deterioration and death to occur after apparent stabilization of the disease with treatment in the hospital for two or three weeks. If the patient does survive, fatty change and acute inflammation may disappear and an amazing degree of hepatic repair may occur under optimum conditions.

BLEEDING

In the patient with hematemesis associated with hepatic disease, all are familiar with advanced hepatic disease in alcoholism manifested

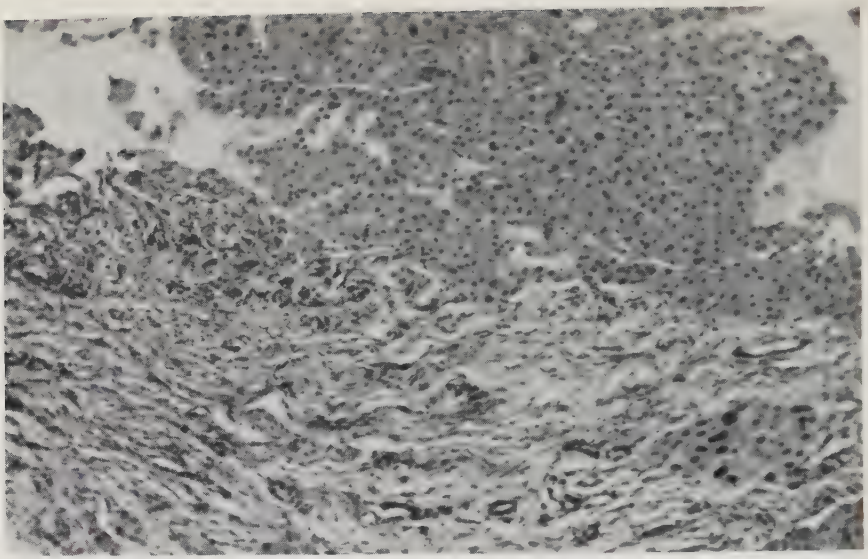

Figure 1. Photomicrograph of needle biopsy of liver taken at operation revealing well marked fibrous bands with regenerative nodules of varying size characteristic of postnecrotic cirrhosis (× 100).

by spider angiomata, liver palms, and increased abdominal collaterals. Hematemesis is common and usually originates from esophageal varices but also from other lesions, such as erosions of the stomach or esophagus or peptic ulcer. Many, however, are unaware that the first clinical evidence of hepatic disease in silent postnecrotic cirrhosis may be an episode of massive hematemesis from varices and that the only clinical evidence suggesting this possibility may be demonstration on physical examination of a small liver as an area of reduced hepatic dullness projected on the anterolateral thoracic and abdominal wall measuring less than 9 cm. vertically. A large spleen may be present, but unfortunately enlargement is variable. Spider angiomata, liver palms, ascites, and other stigmas are usually absent, and even more disconcerting, all laboratory estimates of hepatic involvement may be normal. In some instances, slight decrease in the level of serum albumin with slight increase in globulin may be the only suggestive laboratory abnormality encountered. Early esophagoscopic examination is imperative, as the patient usually has good liver function and is an ideal candidate for emergency portacaval shunt. Microscopic section of the liver reveals mature, hardened, fibrous tissue in the liver with little or no cellular infiltration, no hepatocellular necrosis, and healthy, regenerated, hepatic parenchyma.

Illustrative of this situation is the case of a 40-year-old man who was seen in 1958 with a history of massive hematemesis 14 months before. Abdominal exploration at that time revealed huge esophageal varices; the coronary veins and other collaterals were ligated.

On examination on admission to the Clinic, the spleen was palpated 6 to 8 cm. below the right costal margin, but the liver could not be felt, and on percussion, measured approximately 6 cm. in extent along the right anterior thoracic

wall. Bromsulphalein retention was 0, thymol turbidity 1.7 units, serum alkaline phosphatase 3.7 units/100 ml., and total serum protein 6.7 gm./100 ml. with 4.3 gm. of albumin and 2.4 gm. of globulin. Total serum bilirubin was 1.25 mg./100 ml., with a directly reacting component of 0.29 mg./100 ml. These results are within normal limits for our laboratory.

At operation, the liver was grossly nodular, and on biopsy broad bands of fibrous tissue, consistent with a diagnosis of postnecrotic cirrhosis, were noted (Fig. 1). Portacaval shunt was done. Pressure in the portal vein before performance of the shunt was 46 cm. of water, and afterwards, 14 cm. of water. The patient was discharged from the hospital on the eleventh postoperative day after an uneventful postoperative course. He did well at home for six weeks, but then again experienced massive hematemesis and melena with progressive hepatic failure, and died. At necropsy a patent portacaval shunt was noted, but an eroded esophageal varix thought to be the site of bleeding was found.

This case demonstrates not only the presence of sufficient hepatic damage to produce portal hypertension and bleeding esophageal varices, despite normal results of liver function tests, but also the fact that adequate decompression is not necessarily absolute insurance against death from bleeding varices.

REGENERATION

A further extreme of the vagaries of postnecrotic scarring and regeneration is presented by an occasional patient with a single abdominal mass, which may be in the epigastrium, left upper abdominal quadrant, right upper abdominal quadrant, or right flank, and which represents a single, large, regenerated, hepatic nodule, usually the only remaining functional hepatic tissue the patient has. Conventional laboratory tests ordinarily indicate modest impairment of bromsulphalein retention and mild alterations of albumin and globulin levels. Hepatic scintillation scanning reveals localization in the mass with little or no concentration in the usual areas of the rest of the liver (Fig. 2). Recognition of this condition is important, as an unwary surgeon

Figure 2. Hepatic scan with radioactive gold showing massive regeneration in area of right lobe and little evidence of activity in other areas.

Figure 3. Photograph at operation showing massive regeneration of right lower portion of liver. The remaining liver was entirely scar tissue.

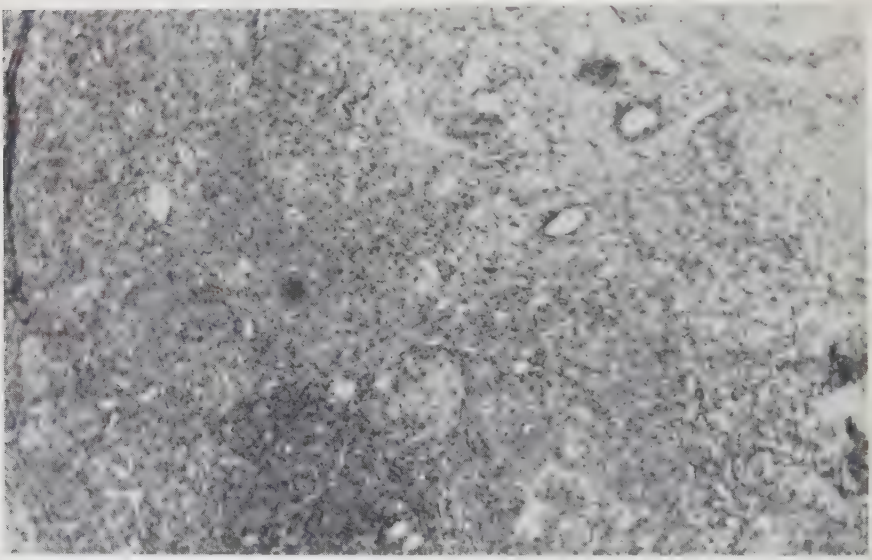

Figure 4. Photomicrograph of biopsy of a portion of the remaining liver other than the nodule showing essentially complete atrophy and fibrosis (× 80).

might unwittingly perform total functional hepatectomy in the belief that he is removing a hepatic tumor.

Such an example is the case of a 34-year-old woman who came to the Clinic in 1949 with a history of loss of energy and mild edema of the ankles of two years' duration. A small mass was noted in the right upper abdominal quadrant.

During the next eight to ten months it grew rapidly until it covered approximately one-half of the abdomen. Since then it has not grown appreciably.

On physical examination a large nontender mass occupying the greater part of the right side of the abdomen was noted. It was most prominent below and to the right of the umbilicus, moved with respiration, and had a sharp left border. Roentgenography revealed the gallbladder to the left of the midline containing a number of calculi. Bromsulphalein retention was 7 per cent at the end of 45 minutes, cephalin flocculation 4 plus, and total serum protein 7 gm./100 ml. with 4 gm. of albumin and 3 gm. of globulin.

Because of uncertainty of the nature of the mass, exploration was performed (Fig. 3). Biopsy from the mass showed moderately severe hepatitis with scarring, and biopsy from the left lobe of the liver showed essentially complete fibrosis (Fig. 4). The mass was thought to represent nodular regeneration of the liver in response to severe injury and necrosis of the remaining hepatic tissue. The patient has remained well in the interim and, when last heard from, 18 years postoperatively, was having no difficulty.

PRURITUS; PLEURAL EFFUSION

Pruritus is another easily recognized symptom of cholestasis, and a hallmark of the jaundice of mechanical obstruction. In patients with early primary biliary cirrhosis or granulomatous infiltration of the liver, however, severe pruritus, lipidemia, and xanthomata may all precede clinical appearance of icterus, and investigation of this symptom should include liver biopsy as well as the conventional liver function tests. The physician should not be diverted by demonstration of a normal total serum bilirubin level.

An occasional presenting sign which may not be attributed to hepatic disease is *pleural effusion* or *hydrothorax*. Most commonly on the right, it may occasionally be the first apparent clinical evidence of fluid retention in cirrhosis of the liver. It is believed to be due to transmigration of lymphatic or ascitic fluid through the diaphragm, but may occur in the absence of demonstrable ascites.

IMPROVEMENT WITH CAREFUL MANAGEMENT

Finally, and perhaps of most importance in the evaluation of patients with hepatic disease is the frequency with which patients with advanced cirrhosis or chronic, active hepatitis, by careful management, become stable and able to live useful lives.

Such a case is that of a 44-year-old man who was originally seen in 1953 because of accumulation of fluid in the abdomen. He had a history of excessive indulgence in alcoholic beverages. On physical examination scattered spider angiomata were noted on the face and chest; wheezing was heard in both lower pulmonary fields. The abdomen was enlarged and ascites was pronounced. The liver was palpated 10 to 12 cm. below the right costal margin, had a sharp edge, and was firm. The impression was that, although the liver was easily felt, its mass might be somewhat reduced. The spleen was not palpated. Bromsulphalein retention was 28 per cent, serum bilirubin 3 mg./100 cc. total, 2.06 mg./100 ml., directly reacting. Serum albumin was 2 gm./100 ml. with globulin 3.7 gm./100 ml. There was moderate anemia (11.5 gm. of hemoglobin, 37.5 per cent hematocrit, 3.5 million/cu. ml. red blood cells, 4,800/cu. ml. which blood cells with 77 per cent segmenters. Urine urobilinogen excretion was elevated to 8.8 Ehrlich

Figure 5. Esophagogram demonstrating moderate sized varices in lower two-thirds of esophagus.

units in two hours. Prothrombin time was extremely low but with administration of vitamin K returned to 50 per cent of normal.

On a program of sodium restriction, nutritious diet, and vitamin supplements, the patient gradually improved and through the years has continued to do well. Approximately four years from the time he was first seen, however, elevation of intrasplenic pressure from 180 mm. of water (a normal figure) to 340 mm. of water was demonstrated, and modest esophageal varices have been seen esophagoscopically and roentgenographically (Fig. 5). He has, however, continued to improve. His last physical examination in 1961 revealed a liver palpated only 4 to 5 cm. below the right costal margin on deep inspiration, a spleen palpated 3 cm. below the left costal margin, and no edema or ascites. The hemoglobin was 15.2 gm., hematocrit 45 per cent, red blood cell count 4.7 million/100 ml., sedimentation rate 15 mm./hour, prothrombin time 14.5 seconds with an 11 second control, total serum protein 6.2 gm./100 ml. with 3.7 gm. 100 ml. of albumin and 2.5 gm./100 ml. globulin. Total serum bilirubin was 1.88 mg./100 ml. with a directly reacting figure of 0.29. Bromsulphalein retention was 21 per cent at the end of forty-five minutes and serum alkaline phosphatase 2.63. Since that time the patient has been followed by mail, is feeling well, working full time in a prosperous grocery business, and has had no bleeding, ascites, or edema.

CONCLUSION

The foregoing observations which have proved helpful in the diagnosis and management of hepatic disease are apparently not widely known. Recognition of some of these facts may facilitate evaluation and management of the problems presented by the patient with hepatic disease.

Colonic and Systemic Manifestations of Chronic Ulcerative Colitis

PHILIP C. YOUNG, M.D.*

The average physician may think of chronic ulcerative colitis as a disease which occurs characteristically in persons of either sex between the ages of 11 and 30 years and is manifested by passage of bright red blood with each bowel movement, passage of bloody mucus, and certain systemic symptoms. The unusual manifestations of the disease may be considered as complications or adverse side effects relating to the colon or other systems of the body.

Colonic complications may threaten life and will determine the course of treatment. Unusual clinical manifestations affecting other systems of the body associated with active or chronic disease are not necessarily related to the severity of the disease. Association of these unusual adverse effects with ulcerative colitis is recognized, but proof of a single cause remains to be established.

The records of 241 consecutive patients with a diagnosis of chronic ulcerative colitis, seen at the Ochsner Clinic and Ochsner Foundation Hospital during the past 25 years, were reviewed in an effort to determine the incidence of complications and unusual clinical manifestations relating to the disease. The patients ranged in age from 4 to 74 years, the majority being between 10 and 30 years of age. There were 105 female and 136 male patients. Although the study covers the period before widespread use of salicylazosulfapyridine, the incidence of complications during the first ten years was similar to that for the last ten years of study.

COLONIC MANIFESTATIONS

In this series pseudopolyp was the most frequently recorded colonic manifestation of ulcerative colitis. This lesion was detected most often radiographically, although a fair number of pseudopolyps was discovered proctosigmoidoscopically. The left half of the colon was the segment most frequently diseased, and the rectum was the region subject to the greatest number of complications. Of the 31 patients

From the Section on Gastroenterology, Ochsner Clinic, New Orleans, Louisiana

with fistulas, 16 had fistula-in-ano, 8 rectovaginal fistulas, 2 rectoperitoneal fistulas, 2 cecal fistulas, and one each fistula in the transverse colon, fistula in the descending colon, and fistula in the ileum. Eleven patients had rectal abscesses, 10 rectal ulcers, and 8 rectal fissures. Five of the rectal abscesses were perianal, one ischiorectal, one presacral, and 4 rectal. Toxic megacolon developed in 7 patients, intestinal perforation in 6, massive hemorrhage in 5, rectal stricture in 4, and colonic obstruction in 3. Cancer of the colon developed in only 2 patients, both of whom died.

COMMENT. The complications of ulcerative colitis have attracted the interest of clinicians for many years, in anticipation that clues to the cause of the disease might be found. Bargen[1] and Edwards and Truelove,[3] who reported larger series of cases than the present series, also noted complications of many systems other than the colon. In the colon, pseudopolyps, fistulas, and strictures are the most frequent complications. Pseudopolyps are found more often in the transverse and descending colon than in the rectum.[2] Stricture resulting from extensive disease of the colon occurs most frequently in the rectum. Fistulas, rectal ulcers, and fissures are seen in both localized and extensive disease of the colon. Carcinoma of the colon develops in a limited number of patients whose disease appeared early in life or has persisted in the chronic state for many years and is extensive.[4] Toxic dilatation of the colon is seen in patients who have had extensive destruction of the layers of the wall of the colon.[6] The likelihood of perforation and peritonitis makes this a serious problem of management.

SYSTEMIC MANIFESTATIONS

Of the systemic effects, arthritis was the most common in the present series, occurring in 31 patients. Arthritis occasionally accompanied the acute attack, but more frequently developed during the chronic stage. Spondylitis was diagnosed in only 4 patients. Cutaneous lesions have often been reported in association with ulcerative colitis. In this series, 19 patients had erythema nodosum at some time during their illness, 5 exhibited pyoderma, and one had bullous lesions of the hands. In 6 patients venous thromboses developed. Ophthalmic lesions were observed in 6 patients; 3 had uveitis, 2 conjunctivitis, and one corneal ulcers.

Liver function tests were not routinely performed, but 4 patients were found to have fatty liver, 2 cirrhosis, and 2 hepatitis. Liver biopsies confirmed the pathologic changes in the liver. Additional incidental side effects recorded were aphthous stomatitis in 4 cases, clubbing of the fingers in 3, growth arrest in 2, and pyelonephritis, pericarditis, nutritional heart disease, angioneurotic edema, and nonspecific perivascular inflammation of the fingertips, in one case each. Only 2 patients were considered to have fulminant disease.

COMMENT. The musculoskeletal system is frequently affected by chronic inflammatory disease of the intestine. Arthralgias, arthritis,

and spondylitis occur sometimes simultaneously but usually after onset of colitis.[9] Arthritis may affect any joint, although the knees and ankles are the most frequently involved. The arthritis rarely leaves significant alteration in the joint space.[8, 9]

Ocular lesions can appear at any stage of ulcerative colitis. They tend to recur with continuation of the colonic inflammation. Nongranulomatous iritis, episcleritis, corneal infiltrates, and corneal ulcers have been observed in association with ulcerative colitis.[5] That the liver would be affected by a disease in the colon seems only reasonable. Fatty infiltration of the liver is considered to be the most common hepatic alteration, but pericholangitis, cirrhosis, and hepatitis are common sequelae of chronic ulcerative colitis.[10, 11, 12] Amyloidosis is an occasional complication of patients with prolonged low grade chronic ulcerative colitis.[7]

The observations of associated abnormalities depend on the interest and the alertness of the attending physician. Whether these are only incidental changes or actual manifestations of a disease affecting many systems will become more evident when the nature and etiology of chronic ulcerative colitis is better established.

SUMMARY

Numerous complications of chronic ulcerative colitis are reported. In addition to the complications affecting the bowel, many systemic manifestations involving the eyes, skin, and musculoskeletal system and liver are noted and should serve as clues to the otherwise unsuspected diagnosis of chronic ulcerative colitis.

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Salmonellosis and Shigellosis: Epidemiology and Clinical Features

F. SCOTT O'NEIL, M.D.

Establishment by the United States Public Health Service of the Salmonella Surveillance Unit in 1963 led to more realistic appraisal of the frequency and importance of salmonellosis in this country. A similar surveillance program is in operation for the study of shigellosis, though its scope is more limited. It was apparent from other sources that the incidences of typhoid fever and bacillary dysentery had declined gradually throughout the century, primarily as a result of improved environmental sanitation. In contrast, the true incidence of nontyphoid Salmonella infections and their relationship to an extensive animal reservoir have evolved only during the present decade; the rising curve emphasizes the relative inability of sanitary improvement to control nontyphoid salmonellosis.[9]

EPIDEMIOLOGY

Occasional patients with Salmonella gastroenteritis and bacillary dysentery, both lacking any unique sign or symptom to differentiate them from the morass of "nonspecific diarrheal disease," pass through the physician's office unnoticed; of much broader significance is the repeated observation that the number of persons who seek medical care represents but a small fraction of the total number of cases of the disease in the community at any given time.

The importance of the human carrier to the general incidence of salmonellosis and shigellosis is unknown, but from consideration of certain epidemiologic differences between members of the two genera, certain generalizations may be made. Apart from the simian primates, man is the only animal known to suffer from shigellosis. Therefore, each case must be acquired from another person, either directly, as between small children at play, or indirectly, as between adults in a crowded institution, such as a jail, where personal hygiene is inadequate. Though food and water supplies are only rarely the cause of Shigella epidemics,

From the Department of Gastroenterology, Ochsner Clinic, New Orleans, Louisiana.

subsequent pollution of streams may be responsible for additional cases.

Certain similarities are apparent between typhoid fever and shigellosis; Salmonella typhosa and all shigellae species are host-adapted and are virtually restricted to the human being. Both diseases imply the existence of human fecal contamination of the environment, and both may be transmitted from a food-handling carrier to otherwise healthy persons. In sharp contrast, however, Salmonella species, and particularly Salmonella typhosa, survive well in unchlorinated water supplies, and, as such, they pose a continuing danger of spawning epidemic disease. Coliform counts and the number of Salmonella isolates begin to rise within a few hours after experimental cessation of chlorination; inadequate chlorination of water supplied to tourist centers leads to typhoid epidemics of worldwide proportions, since infected persons may travel to any point on the globe during the incubation period of the disease.[1] Seepage of unchlorinated river water into cans of processed meat during cooling led to a major typhoid epidemic in 1964.[2, 9]

A large animal reservoir exists among species of the genus Salmonella, exclusive of Salmonella typhosa. When isolates from animal sources are compared with those from human sources, the ten most frequently isolated species from the one are strikingly similar to the other, apart from the host-adapted species, Salmonella typhosa and Salmonella pullorum. Salmonella typhimurium is by far the most frequent species isolated from both animals and man, not only in the United States but in Canada as well. Concerning studies in the United States, the animal isolates are mostly from poultry, and should other domestic animals be studied with equal intensity, the profile might not match so well that from human sources as previously mentioned.

All nontyphoid Salmonellae appear to be pathogenic to poultry, particularly to young chicks. Those that survive enter maturity as permanent asymptomatic carriers. Such infestation is not of economic importance to the poultry farmer, since it does not impair egg production or affect nutrition and growth. Of great public health significance are the fecal contamination of the egg surface, the penetration of Salmonella into the interior after inadvertent cracking during processing, and the cross-contamination of other eggs in the water bath used to clean the surface. Careful inspection of top quality eggs may reveal large numbers of cracked eggs, many of which are fecally contaminated.[6] Contaminated egg liquid can be pasteurized without damage to the product, and in food establishments such treatment is now required by law in the United Kingdom; also, baking and dry scrambling of eggs are both effective in eradicating Salmonella.

The gross contamination of abattoirs and poultry processing plants continues despite the best efforts of management and public health veterinarians. Maintenance of large animal reservoirs depends to some extent on use of contaminated protein supplements in animal feeds, and this in turn, to the contamination of rendering plants which supply the ingredients to feed mills.

Entry of infected meat and eggs into retail outlets is often associated with contamination of machinery and other equipment and with inadvertent infection of employees; this leads to contamination of other foods with consequent growth of the outbreak.

CLINICAL FEATURES

Any attempt to categorize Salmonella and Shigella diseases into species-specific types is beset with several difficulties. All species of Salmonella are capable of entering the blood stream, and in addition many instances of Shigella bacteremia have been reported. Typhoid-like syndromes are on record with Shigella and nontyphoid Salmonella infections, though they are especially rare in the former. Finally, typhoid and paratyphoid bacilli may give rise to asymptomatic infections, or to others characterized by gastroenteritis with brief or inapparent fever.

Systemic Salmonella infections are characterized by fever, headache, abdominal pain, splenomegaly, and rose spots. The full picture is presented by few patients; the spleen, though it may be considerably enlarged, is often soft and difficult to palpate. In adults the rose spots are commonly transient or absent altogether. Bradycardia and leukopenia are more often absent than present.

In Salmonella gastroenteritis and in bacillary dysentery, symptoms last only a few days, and only a minority of patients seek medical help. Nearly one-half of all cases occur in children younger than four years of age. Some cases of Salmonella gastroenteritis proceed to systemic proportions with features as mentioned in the preceding paragraph; despite comparable degrees of fever, children with bacillary dysentery are much more prone to convulsions than are children with Salmonella infections.

As is true in many other infectious diseases, the diagnosis is made in the laboratory. Blood and fecal cultures are essential, and multiple specimens may be required. The fluorescent antibody technique has been adapted to certain Shigella infections, but in others the usual culture methods are no more time-consuming and are to be preferred. Measurements of typhoid and paratyphoid agglutinins are useful in the diagnosis of those infections caused by S. typhosa, S. paratyphi A, and S. paratyphi B, but only serial determinations showing a rising titer can be considered diagnostic.

Bacilli of the genus Shigella are more perishable than the Salmonellae, particularly in excreta. Salmonellae are readily recovered from raw sewage effluents, whereas Shigellae are only rarely cultured from this medium. A delay of two hours in culturing rectal swabs may decrease by one-half the possibility of recovering Shigellae.[8] Finally, many media commonly used in the bacteriology laboratory for isolation of enteric pathogens are, in fact, not ideally suited for isolation of Shigellae; any Shigella isolated from the popular selenite F. broth and SS agar system might be said to have survived a biochemical obstacle course.[7]

SUMMARY

Salmonellosis and Shigellosis are frequently encountered illnesses, though many cases are unrecognized because of failure of the patient to consult a physician and because of the nonspecific and self-limited course of the disorder. The fastidious nature of Shigella species is associated with poor recovery in the laboratory and with limited survival in raw sewage and in unchlorinated water supplies. The more hardy Salmonella organisms pose a continuing threat of epidemic disease by their ability to survive in inadequately treated water supplies. The nontyphoid Salmonellae share a vast animal reservoir from which human disease stems; most foods from animal sources may be rendered free of contamination by cooking, or, in the instance of liquid egg, by pasteurization.

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Uncommon Manifestations of Rheumatoid Arthritis

THOMAS E. WEISS, M.D.

KARL E. KELLER, M.D.

Variations in the classical clinical picture of rheumatoid arthritis, while numerous, are familiar to most physicians. The unusual manifestations may involve many systems and may discommode the attending diagnostician.

The typical feature of rheumatoid arthritis is slowly progressive, bilateral, polyarthritis with subcutaneous nodules about the elbows. These patients complain of stiffness in the morning, fatigue in the afternoon, and lassitude. Exacerbations and remissions with stepwise loss of articular mobility are common. Normochromic normocytic anemia, elevation of the erythrocytic sedimentation rate, and positive findings from serologic tests for rheumatoid arthritis are the usual results of laboratory tests. Radiologic changes in most of these patients range from periarticular demineralization to narrowing of the articular space and destructive bony changes or ankylosis.

UNCOMMON SYSTEMIC MANIFESTATIONS

An acute febrile course or a prolonged period of malaise and fever with minimum articular symptoms may characterize the onset of rheumatoid arthritis in 10 to 15 per cent of patients. A pattern of recurring, incapacitating acute attacks of monoarticular arthritis lasting only a few days, subsiding without residual effects, and unassociated with abnormal results of laboratory studies is sometimes seen in patients with rheumatoid arthritis. This pattern of palindromic rheumatism eventually takes on features of definite rheumatoid arthritis. In juvenile rheumatoid arthritis the patient may experience an acute febrile clinical course with debility, sweats, prostration, rash, and leukocytosis. Variations of this clinical pattern in adult rheumatoid arthritis occur in less than 30 per cent of patients, and when fever and leukocytosis are

From the Department of Internal Medicine, Ochsner Clinic, New Orleans, Louisiana

the predominating symptoms with insignificant articular involvement initially, the condition is usually mistaken for an infectious process.

UNCOMMON MANIFESTATIONS IN THE HEAD AND NECK

Ocular lesions may develop before or after attacks of rheumatoid arthritis. Recurring iritis or iridocyclitis, the most common ocular complications, occur in approximately 35 per cent of patients with rheumatoid arthritis. Rheumatoid nodules may appear on the sclerae (Fig. 1), and band-shaped opacities of the cornea or scleromalacia perforans may occur. Blindness is a possible end result of this complication. Features of Sjögren's syndrome, such as a slight ocular sicca syndrome, keratoconjunctivitis sicca or dry eyes, and dry upper respiratory passages due to atrophy of the mucous secreting glands, are found in 10 to 15 per cent of patients with rheumatoid arthritis. Before or after the ocular complications become severe, the patient may be troubled with prominent enlargement of one or more of the lacrimal or salivary glands due to pronounced periductal lymphocytic infiltration. These glands are usually hard, nontender, resistant to treatment, and disconcerting to both the patient and the physician.[10]

Patients sometimes think they have "ear trouble" because of pain in and about the ears. A few patients also complain of pain arising from their molars. This often is the result of temporomandibular joint synovitis, which is a part of the rheumatoid arthritic process and is demonstrated by eliciting synovitis in the temporomandibular articulation. Changes in this joint may also be evident roentgenographically.

Equally confusing is the complaint of "sore throat," which, when investigated, proves to be soreness in the region of the upper lateral part of the larynx. This complaint may be due to rheumatoid involvement of the cricorarytenoid joint, the only true joint in the larynx. Synovitis in this small joint may result in serious complications because, when inflamed and immobilized, motion of the vocal cord is reduced and midline fixation may result. If this complication is bilateral, the airway

Figure 1. Nodular lesion in upper temporal area of right eye of 57-year-old woman with classical rheumatoid arthritis.

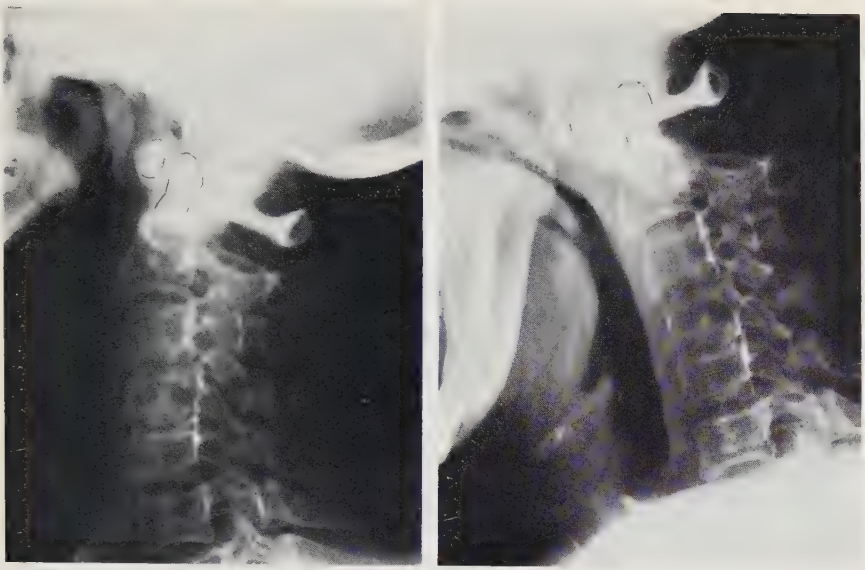

Figure 2. Roentgenogram of 57-year-old woman with classical rheumatoid arthritis showing odontoid process in normal anatomic position (left) and odontoid process swinging posteriorly when neck is flexed (right).

becomes obstructed, respiratory embarrassment occurs, and in rare situations death can result. Patients with rheumatoid arthritis who have respiratory distress, hoarseness, and inspiratory stridor, should be examined for fixation of the vocal cord associated with cricoarytenoid arthritis. Narrowing of the glottic clink from 7 to 4 mm. can mean respiratory distress.[11]

Involvement of the cervical spine is common in the early stages of juvenile rheumatoid arthritis, but uncommon in early adult rheumatoid arthritis. In the latter instance, cervical involvement can cause severe, persistent, occipital headache or cervical pain due to involved nerve roots. This may occur in the absence of peripheral joint arthritis. Pain from high cervical involvement is referred to the retro-orbital, temporal, and occipital areas. In more advanced rheumatoid arthritis, atlanto-axial dislocation due to stretching or rupture of the odontoid ligament may result in serious complications from pressure on the spinal cord (Fig. 2). An end result of such a complication may be spastic tetraplegia and sensory loss.[1]

In some patients with minimal or no involvement of peripheral joints, the intervertebral disks may be destroyed as the result of rheumatoid discitis. Rheumatoid pachymeningitis has caused compression of the cervical cord with neurologic complications.[3]

UNCOMMON THORACIC FEATURES

A patient with rheumatoid arthritis may experience pain and swelling of one or both sternoclavicular joints, the costochondral junc-

tions, or the sternal angle. Pain may be localized and severe and cause difficulty in differential diagnosis if only one joint is involved.

Although postmortem studies on the hearts of patients with rheumatoid arthritis have shown significant cardiac disease attributable to the rheumatoid process, during life heart disease is recognized rarely. Complicating active pericarditis, aortic stenosis, myocarditis, and granulomatous injury associated with rheumatoid arthritis may, however, require specific therapy. It cannot be assumed that these conditions do not become clinically evident in patients with rheumatoid arthritis.

An unusual case of rheumatoid pancarditis thought to represent rheumatoid disease with systemic manifestations but no specific articular disease has been described.[7] In a rare patient acute pericarditis precedes the clinical features of rheumatoid arthritis by several months.[2]

Constrictive pericarditis is not necessarily a complication of chronic rheumatoid arthritis. It can result in cardiac failure that does not respond favorably to the usual treatment but necessitates pericardiectomy.[6] Rarely, complete atrioventricular heart block results from rheutoid involvement of the cardiac conduction system in patients with ankylosing spondylitis or rheumatoid arthritis.[4] This same type of rheumatoid activity may also damage the elastic tissue of the aortic root causing aortic valvular insufficiency. This complication produces severe symptoms in patients with spondylitis but usually is mild in the patient with rheumatoid arthritis.

Respiratory symptoms are uncommon in patients with rheumatoid arthritis, but pulmonary abnormalities are sometimes demonstrable by roentgenography or pulmonary function studies. Pleurisy, with or without effusion, and diffuse interstitial pulmonary fibrosis are the most common respiratory manifestations in these patients.[5] The pulmonary disease usually becomes evident after the arthritis has become active but occasionally it appears as the initial acute process. Rarely is it the cause of dyspnea, unless it is extensive and associated with far advanced or active rheumatoid changes in the joints. There is no definite entity of "rheumatoid pulmonary fibrosis," although interstitial pulmonary fibrosis is associated with some cases of rheumatoid arthritis with hemosiderosis, and pulmonary concretions have been described in two patients.[8]

Rheumatoid arthritic nodules have been demonstrated in the lungs of a few patients, both with and without evidence of classical rheumatoid arthritis of the joints. The rheumatoid nodules may disappear with intensive adrenal steroid therapy but usually recur in the same anatomic location with cessation of such treatment. Rheumatoid nodules in the lungs are usually multiple and some may cavitate. In Caplan's syndrome nodules with pneumoconiosis are sometimes demonstrated in roentgenograms of the lungs of coal miners with rheumatoid arthritis. When pleuritic pain in the region of the diaphragm arises in a patient with rheumatoid arthritis-like symptoms, it is useful to search further for objective evidence of lupus erythematosus.

UNCOMMON ABDOMINAL MANIFESTATIONS

The spleen is palpable in 7 to 10 per cent of patients with rheumatoid

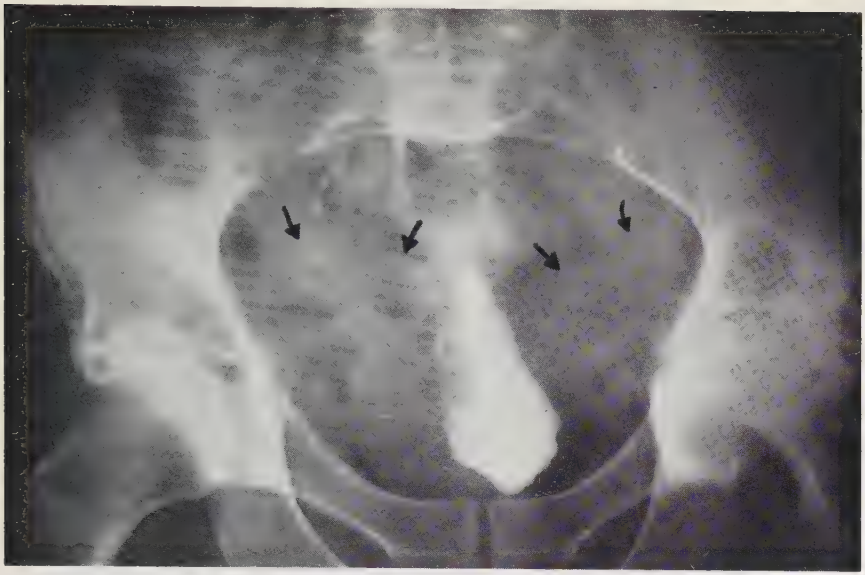

Figure 3. Roentgenogram of 43-year-old man with a 23-year history of rheumatoid arthritis showing a small bladder compressed between soft masses on both sides of the pelvis. Rheumatoid arthritis in left hip; right hip minimally diseased.

arthritis. The presence of chronic rheumatoid arthritis, leukopenia, fever, wasting, and brown pigmentation of the skin in splenomegaly fulfills the diagnostic requisites of Felty's syndrome. About 50 per cent of these patients have a firm, nontender spleen which may extend 2 to 6 inches below the left costal margin. The microscopic changes in the spleen are not specific.

From 10 to 15 per cent of patients with ulcerative colitis or ileitis have arthritis, which in part resembles rheumatoid arthritis. A distended rheumatoid cyst arising from the ileofemoral joint may extend into the pelvis and appear as a mass in the region of the prostate, lower sigmoid colon, or presacral area.[12] (Fig. 3). Such a synovial mass may extend anteriorly, and because of the overlying femoral artery, may suggest a pulsating vascular lesion. If the cyst contains old bloody fluid, the diagnostic difficulty is increased. Pigmented villonodular synovitis can be found in such a synovial lining and when the diagnosis is dependent on a frozen section biopsy at operation, an incorrect diagnosis may result.

UNCOMMON CUTANEOUS, NEUROLOGIC, AND VASCULAR CHANGES

Psoriasis occurs in 3 to 5 per cent of patients with rheumatoid arthritis. These lesions are not localized over the distal interphalangeal joints, as in psoriatic arthritis, and such patients have positive results of rheumatoid serologic tests. Rheumatoid nodules on the elbows and fingers are easily recognized, but those with ulceration that may appear at pressure points on the ears and occiput may cause some confusion.

Peripheral neuropathy occurs rarely in patients with rheumatoid

arthritis, unless they have been treated with adrenal steroids. Peripheral neuropathy is associated with adrenal steroid aggravation of vasculitis, and the extent of symptoms may be out of proportion to the general clinical picture. Patients complain bitterly of numbness and tingling of the toes and fingers, which tend to extend up the limb. Relief of symptoms is often not obtained for many months. Failure of immediate relief of symptoms upon cessation of adrenal steroid treatment again adds to confusion in management of the patient.

Entrapment of the median nerve in the carpal tunnel due to rheumatoid swelling at the wrist is one of the causes of the carpal tunnel syndrome. It may be associated with pain in the hand and forearm that is often worse at night. Tingling and numbness of the palmar aspect of the thumb, index, and middle fingers may occur. The thenar muscles may atrophy with resultant weakening of abduction of the thumb. This clinical manifestation sometimes occurs well before other symptoms of rheumatoid arthritis are evident. Ulnar compression neuritis at the wrist due to edema secondary to rheumatoid arthritis may cause pain extending to the fourth and fifth fingers and forearm. This sometimes occurs in patients also with the carpal tunnel syndrome.

Rheumatoid involvement of the elbow joint results in pressure symptoms at the site of the ulnar nerve. Extensive synovitis of the knee may also result in irritation of the lateral popliteal nerve.

Vasculitis with small areas of cutaneous gangrene or ulceration or a painful nodular lesion on the extremity occurs infrequently in patients with rheumatoid arthritis who have not been treated with adrenal steroids. This complication becomes more evident and more complex in patients with rheumatoid arthritis who have received large doses of adrenal steroids, particularly if the dosage has fluctuated over a prolonged period of time. The ulcerated vasculitis is extremely difficult to manage and may result in gangrene of a digit, hand, or foot. A rare case of comparable gangrene of the digit or hand has occurred in patients with rheumatoid arthritis who have not received adrenal steroids, so that steroids cannot be held totally responsible for such a complication. The severe neuropathy associated with necrotizing angiitis may result in peripheral weakness and loss of sensation in the involved extremity.

UNCOMMON ARTICULAR AND PERIARTICULAR MANIFESTATIONS AND OTHER UNUSUAL FEATURES

Acute synovial rupture can occur in the posterior compartment of the knee joint just lateral to the medial head of the biceps. In some patients with this complication articular fluid may be aspirated from the calf. Pain in the calf, swelling, and tenderness are severe and resemble in part the clinical picture of deep venous thrombosis or phlebitis.

Synovitis of the knee sometimes causes a Baker's cyst. It is not always appreciated, however, that the calf of the leg may be affected without significant involvement of the popliteal area. This is due to extension of the synovial lining into the calf muscles. Symptoms may

result from swelling, tenderness, and possibly pressure on nerves in the area.

Excessive use of a rheumatoid arthritic knee made painless by repeated intra-articular injections of adrenal steroid may result in severe destructive changes similar to those of neurogenic arthropathy. Edema of the legs, and less often the hands, may occur in patients with rheumatoid arthritis. The cause of swelling is not apparent.

Destructive lesions of the bony component of large joints, due to rheumatoid granulomatous activity at the site, may give a radiographic impression of a malignant lytic lesion. This process may also simulate aseptic necrosis of the femoral head and cause destructive lesions of the vertebral bodies. Collapse of a vertebral body by the rheumatoid granulomatous process has been observed by one of us (K. E. K.).

Rupture of a tendon due to rheumatoid granulation reaction in and about the tendon and its sheath may cause sudden loss of use of a digit. This occurs most frequently from rheumatoid pannus activity about the wrist.

A late phase of rheumatoid arthritis which is sometimes unfamiliar to the physician is *amyloidosis*. About 20 per cent of patients with chronic rheumatoid arthritis show amyloidosis at necropsy. Adequate clinical examination during life may reveal this condition in the form of hepatomegaly. Cardiomegaly with congestive heart failure may also occur in such patients. These patients frequently have severe hypoproteinemia and azotemia. A more unusual manifestation of this problem is accumulation of amyloid in the larynx, trachea, and ducts of the sinuses causing symptoms in these areas. Involvement of the esophagus may cause dysphagia, and gastric infiltration may produce symptoms suggestive of duodenal ulcer. Intestinal amyloidosis has produced ileus and malabsorption syndrome in some patients with late stages of rheumatoid arthritis.

UNCOMMON LABORATORY CHANGES

Anemia in patients with rheumatoid arthritis is common and sometimes suggests an iron deficiency, but seldom does administration of iron prove effective unless there is gastrointestinal hemorrhage, probably secondary to complications of therapy. Macrocytic anemia associated with megaloblastic changes in the bone marrow of patients with rheumatoid arthritis has been reported.[9]

Leukopenia can be striking and is usually associated with Felty's syndrome. An occasional LE cell may be seen in 12 to 20 per cent of patients with rheumatoid arthritis, but this does not mean that these patients have lupus erythematosus. Hypoalbuminuria may be due to hepatic dysfunction or localization of albumin in inflamed joints.

Many unusual features underscore the extent of rheumatoid arthritis. To the physician who cares for large numbers of patients with this disease, the atypical features become typical.

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Cervical Root Syndrome

HAROLD M. HORACK, M.D.

The clinical manifestations of the cervical root syndrome may mimic the symptoms of coronary artery disease so closely that errors in diagnosis are common. Complaint of pain in the left side of the chest and arm is insufficient grounds for making a diagnosis of coronary artery disease.

At the meeting of the American Heart Association in Miami in 1965, Dr. H. J. L. Marriott, discussing ventricular arrhythmias, stated that some rhythms might appear to be of ventricular origin, whereas, in reality, they were not—they simply looked that way. Turning to the moderator, Dr. J. Willis Hurst, Dr. Marriott continued, "If I were to see him walking down Collins Avenue with a willowy blonde, I might infer that she was his wife, but inference by assumption or association is a hazardous pursuit."

Dr. Marriott's statement is as applicable to the causal deductions that are made by many physicians as it is to some deductions that might be made on Miami Beach. Proper appreciation of its implications will enable qualified internists to differentiate cardiac pain from the "cardiac-like pains" of extracardiac origin. Time is required, as well as meticulous evaluation of the patient's history, physical findings, and laboratory data. Inasmuch as the diagnosis of coronary artery disease is often made by inference rather than documentation, patients with symptoms suggestive of coronary artery disease should be seen and their problems critically reviewed by a competent medical specialist. A study by Masters and associates[7] emphasizes this point; among 1000 consecutive patients seen in cardiac consultations, 40 per cent had no organic heart disease. Harrison[3] made another poignant observation: "Heaven help the patient who has some minor cause of chest pain plus innocent T wave inversion and consults a physician who takes a rapid and casual history." The same is true of evaluation of the significance of roentgenographic, enzymatic, and all other laboratory data.

For this reason, I reviewed my experience with patients who consulted me because of symptoms that had been interpreted as being due to coronary artery disease but in reality proved to be due to the cervical root syndrome. It has been my impression that this syndrome is the most

From the Section on Cardiology, Ochsner Clinic, New Orleans, Louisiana

common cause of "coronary-like pain" of extracardiac origin. This radicular syndrome should be distinguished from midline cervical disk, neurovascular and other "thoracic outlet" syndromes. Similarly, these syndromes must be differentiated from other disorders that may mimic coronary artery disease, a partial list of which includes esophageal spasm, hiatal hernias, biliary disease, ulcerative disease of the stomach or duodenum, the splenic flexure syndrome, the hyperventilation syndrome, pulmonary embolism, pleurisy, pericarditis, spontaneous pneumothorax, anxiety states, and iatrogenic heart disease.

Masters and co-workers,[7] Harrison,[3] and Marriott[5] have long been exponents of the necessity of differentiating pain of cardiac origin from that of extracardiac origin. They have urged physicians and medical students to avoid making a diagnosis of coronary artery disease by inference, assumption or casual association. Jackson[4] described the cervical root syndrome in great detail, both anatomically and etiologically. Davis'[1] monograph details its clinical aspects. Gorlin's[2] observations on the pathophysiology of cardiac pain reemphasize the importance of a critical examination of the history and laboratory data before a diagnosis of coronary artery disease is justified.

Among atypical manifestations of coronary artery disease are middorsal pain; pain only in the arms, neck, or jaw; pain in the right upper abdominal quadrant or epigastrium; sense of suffocation; tightness in the throat; pain in the chest and arm only when the patient is at rest; coronary pain relieved by exercise; and pain that subsides if the patient stops walking and belches. Patients with angina rarely complain of precordial, left pectoral, or left lateral thoracic pain; the pain or discomfort is almost always in the middle of the chest. The same is true of patients with myocardial infarction, unless the infarction is associated with pericarditis. Electrocardiographic studies (including monitoring), selective enzymatic determinations, and careful clinical observations will usually provide information which will enable the physician to differentiate coronary artery disease from disease of extracardiac origin. Occasionally, right and left coronary angiographic studies are necessary to determine whether the patient has coronary artery disease. These are points that Davis[1] did not mention or emphasize in his otherwise excellent monograph. If the physician realizes that other conditions may mimic coronary artery disease, many errors in diagnosis can be avoided, and many patients can be spared needless hospital expense, loss of income, invalidism, loss of opportunity for promotion, loss of insurability, or even enforced retirement. An iatrogenic-induced illness, as it is related to heart disease, may have tragic consequences, including suicide and lesser crimes.[6]

THE CERVICAL ROOT SYNDROME

The cervical root syndrome is a recognized entity. Because it may at times so closely mimic coronary artery disease, it is unfortunate that its importance has not been documented in all medical textbooks, or, more often, in published medical reports.

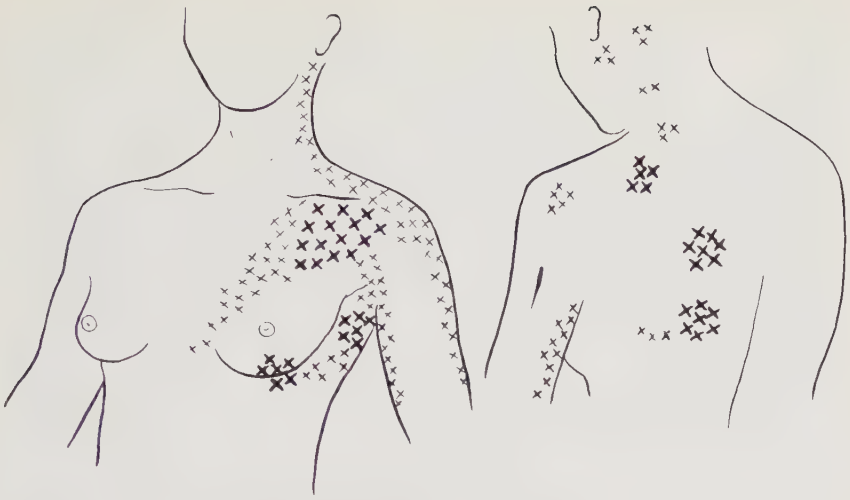

Figure 1. Diagrammatic representation of the distribution of the pain associated with the cervical root syndrome. The heavy markings indicate the areas to which the most intensive pain usually is referred.

Most patients with the cervical root syndrome are between 30 and 60 years of age. Exceptions are encountered who are younger or older. The ratio of men to women is about two to one. A history suggestive of angina or myocardial infarction is more suspect in the patient with a strong family history of coronary artery disease, or in the female patient who is a castrate or of postmenopausal age. Anxiety, tension, apprehension, and neurotic manifestations must be carefully assessed. The same is true in the evaluation of a history of injury to the head, neck, or chest. Many patients with the cervical root syndrome complain of "shortness of breath." This symptom is not true dyspnea but is occasioned by the fact that taking of a deep breath necessitates the use of the accessory muscles of respiration, and this, in turn, intensifies the discomfort experienced in the chest, arm, and back. Often the patient with the cervical root syndrome may relate occurrence of symptoms to certain positions of the head or neck, changes in posture, or use of the arms. Most patients complain of tenderness on palpation in areas of referred pain, particularly in the anterior or posterior thoracic wall. The character of the pain ranges from mild paresthesias to agonizing discomfort in the chest, shoulder, or affected arm, usually the left. The intensity of the pain tends to wax and wane. Its duration is variable, lasting for only a few minutes or several hours or persisting for days or weeks. Because this is a radicular syndrome that involves the cervical nerve roots, cervical plexus, or both, the pain may be sharply localized or referred to many areas (Fig. 1).

Etiologic Factors

The most common causes of symptoms are severe tension and degenerative disease of the lower cervical intervertebral disks asso-

ciated with formation of osteoarthritic spurs that encroach on the neural foramina. Occasionally, a history of injury to the head or neck (including whiplash injuries) may be obtained. The factors causing tension or anxiety are usually apparent or can be elicited.

Because many of these patients believe they have coronary artery disease, or because this idea often is encouraged by an expression of opinion by their physician, they are prone to relate the pain in their chest and arm to exertion. Careful questioning will reveal that their symptoms are not invariably and specifically related to the expenditure of energy or to other factors conducive to myocardial hypoxia. This syndrome is similar to that of Heberden's angina only to the extent that certain specific types of activity may provoke "atypical" angina-like pain. Commonly, they are associated with activities that result in relatively acute flexion of the cervical spine or with use of the arms. Patients with uncomplicated cervical root syndrome ordinarily can climb flights of stairs or walk for miles (even in the wind and cold) without experiencing symptoms that would ordinarily be associated with the diagnosis of "angina of effort." On the other hand, women who complain of pain in the chest or arm when they sweep, mop, raise windows, hang up clothes, carry groceries, read in bed, or sleep on a bolstered pillow may suspect that the pain is due to organic heart disease. They often become alarmed because the pain occurs at "rest" or may awaken them from sleep. The same is true of men who experience pain in the left side of the chest and left arm on stooping or lifting heavy objects, or whose occupation necessitates acute or prolonged flexion of the cervical spine or use of the arms in a position of hyperabduction.

Men and women whose "angina-like" symptoms are due to the cervical root syndrome seldom experience discomfort during or immediately after intercourse. To my knowledge, the differential significance of this clinical observation has not been documented. Metabolic, physiologic, and electrocardiographic observations, however, have been recorded during the act of intercourse, and lend credence to the concept that angina under these circumstances is an "effort" syndrome.

Physical Signs

Ordinarily, the only physical sign is a palpable increase in the degree of muscle spasm at the root of the neck. Occasionally, venous distention may be noted on the affected side. Application of digital pressure over the lower cervical nerve roots on the affected side will usually completely or partially reproduce the symptoms. If the patient has pain at the time of the examination, manual traction applied to the head may afford temporary relief. Occasionally, during or after traction the pain may be intensified. Either of these observations should lead one to suspect that symptoms are referable to the neck rather than the heart Persistent neurologic or vascular abnormalities are not associated with the uncomplicated cervical root syndrome. For this reason the Adson, costoclavicular, and hyperabduction maneuvers usually yield negative results. The same is true of symptoms that at times are provoked by acute flexion of the cervical spine or fist percussion applied to the vertex of the skull.

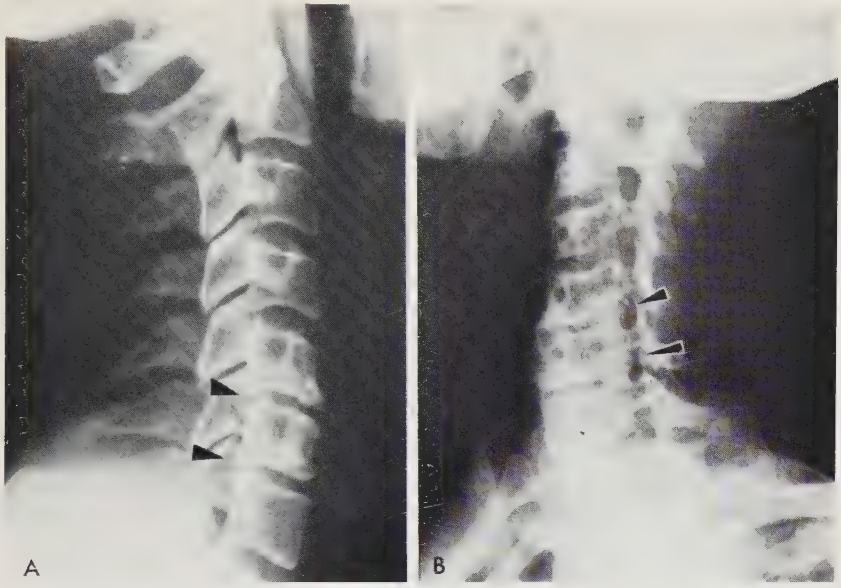

Figure 2. Roentgenogram shows narrowing of intervertebral disk, spur formation, and straightening of the cervical spine. Such changes are seen in patients with the cervical root syndrome. The patient's history suggested a diagnosis of severe angina. The resting and exercise electrocardiograms showed no abnormalities. Coronary angiograms revealed severe coronary occlusive disease just distal to the origin of the left coronary artery. Myocardial revascularization resulted in relief of symptoms. *A*, Lateral view. *B*, Left oblique view.

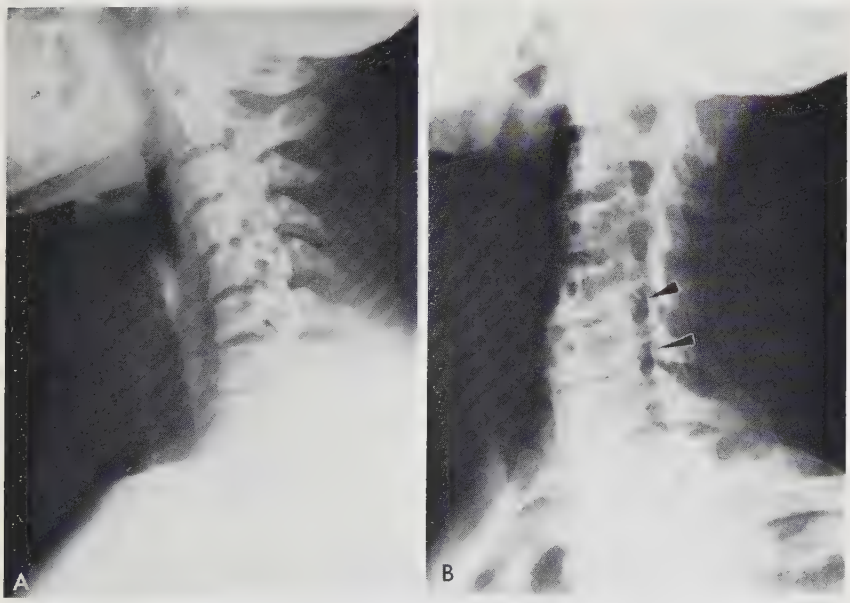

Figure 3. This patient was acutely upset as the result of a recurring domestic problem. Note reversal of the normal cervical lordotic curve due to intense muscle spasm. *A*, Lateral view. *B*, Left oblique view.

Laboratory Studies

The electrocardiogram shows no abnormalities unless the patient has or has had heart disease. Serial electrocardiograms and enzymatic determinations usually will suffice to differentiate cardiac from extracardiac pain. Similarly, roentgenography of the cervical spine, including oblique views, is essential to differentiate the two kinds of pain. Roentgenograms almost invariably show evidence of degenerative disease of intervertebral disks, osteoarthritic spurs encroaching on the neural foramina, and loss of the normal lordotic curve due to muscle spasm. Though the roentgenograms are of diagnostic importance, they must be critically interpreted in the light of all other clinical and laboratory data (Fig. 2). In the purely functional disturbances, there may be no structural changes, but only roentgenographic evidence of intense spasm of the muscles of the neck (Fig. 3).

Treatment

Treatment will not be detailed here. It should be noted, however, that when physical therapy is prescribed, emphasis should be placed on cervical traction with the patient sitting and his head and neck slightly flexed. As much as 40 to 50 pounds can be applied for brief periods; for periods up to 30 minutes, 20 to 25 pounds is well tolerated. During the initial phases of physical therapy, some patients may complain that treatment aggravates symptoms. This is a "rebound" phenomenon and usually comes on shortly after completion of a treatment. If symptoms continue to worsen and, more specifically, are associated with objective evidence of a neurologic disorder, physical therapy should be discontinued immediately, and the patient should be seen in consultation with a neurologist or a neurosurgeon because of the possibility that treatment may have aggravated other disease of the cervical spine. Insofar as possible, this possibility should have been excluded before therapy was instituted. During the past 20 years, I have had no occasion or reason to recommend any of the surgical procedures that have been suggested for the relief of the symptoms attributable to the cervical root syndrome.*

CORONARY AND CORONARY-LIKE DISEASE IN OFFICE PRACTICE

To determine the incidence of the cervical root syndrome, records of the first 50 patients seen in my office during the months of January, April, July, and October, 1965, were reviewed. It was believed that such a selection would constitute a fairly representative sample of the patients seen by internists with a special interest in cardiology. In this group of 200 patients, 151 had, or thought they had, organic heart disease. The other 49 patients consulted me for reasons ranging from premarital examinations to acute febrile illnesses, and a number of patients

*Since this was written, one patient has had the Coward procedure.

with obviously surgical conditions. Among the 151 patients were 55 who had had myocardial infarcts and 37 who had angina. Only 11 patients (20 per cent) with previous attacks of myocardial infarction also had angina. In this same 151 patients were 35 (21 per cent) in whom a diagnosis of the cervical root syndrome was made. Three (5.5 per cent) of the patients with angina, and 6 (11 per cent) who had had myocardial infarcts, also had the cervical root syndrome. Eighteen of the 151 patients (13 per cent) had disturbances of rate or rhythm which were of concern to them. Eight (4 per cent) of this same group had esophageal spasm, and 7 (3.5 per cent) had hiatal hernias. In this series of 151 cases, there were, of course, isolated instances of pericarditis, myocarditis, cholecystitis, cholelithiasis, and malignant and ulcerative disease of the esophagus, stomach, and upper gastrointestinal tract.

DISCUSSION

This random and limited survey confirms a number of opinions that I have entertained for a long time. First, a diagnosis of coronary artery disease can be documented in only about 50 per cent of patients who state that they have had myocardial infarcts or have angina. The remainder have "cardiac-like pains," disturbances of rate or rhythm, or other symptoms suggestive of, but unrelated to, coronary artery disease. Secondly, the cervical root syndrome is the most common cause of the pain and other symptoms that may mimic angina or myocardial infarction. Finally, a significant number of patients with unequivocal evidence of coronary artery disease, past or present, also have symptoms compatible with a diagnosis of cervical root syndrome. This was true in 11 per cent of the 81 patients in this group who had angina or had had myocardial infarcts.

The importance of these observations is obvious. Patients with known coronary artery disease are naturally more concerned and anxious about any pain or discomfort in their chest or arms than are those whose symptoms only mimic coronary artery disease. Occasionally, an attack of severe angina may provoke the cervical root pain. The converse also is true. When the symptoms of angina or infarction with or without the cervical root syndrome coexist, the physician who takes the casual history and makes a "snap" opinion may render his patient a gross disservice. To differentiate the symptoms due to coronary artery disease from those due to other factors requires time and meticulous attention to all diagnostic details. Sometimes the differentiation can be made in the office or at the bedside; sometimes it requires hospitalization for definitive studies and observations, including selective coronary angiographic studies. Once the precise nature of the patient's symptoms is ascertained, corrective or supportive measures can be instituted.

SUMMARY

Inference by association or assumption is, indeed, a hazardous pursuit. This is especially true in the field of cardiology. To make a

diagnosis of coronary artery disease when it does not exist can have dire consequences; the converse is also true. The clinical manifestations of the cervical root syndrome may mimic coronary disease and its diagnosis should be considered if the patient's symptoms and electrocardiographic and other laboratory studies are not consistent with the diagnosis of coronary artery disease.

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The Varying Picture in Gout

RICHARD K. LANGE, M.D.*

Podagra in its classical form is not a problem in diagnosis. Gout may, however, have manifestations atypical enough to mimic other diseases. The clinician must maintain a high index of suspicion to detect gout in its less classical appearance. He must be familiar with these unusual manifestations if he is to recognize cases which he encounters.

CLASSICAL PICTURE

A typical attack of gout occurs in a middle-aged man as acute monarticular arthritis. The affected joint is swollen, red, hot, and exquisitely tender. The patient may have had similar previous attacks, usually in the great toe. He is asymptomatic between attacks. Systemic symptoms are minimal except for variable fever. The usual attack is not associated with morning stiffness or fatigue.

A detailed history of the present illness may bring out significant points that will remove a problem from the atypical to the typical. The physician should consider the possibility of gout even though there is already one existing reason for the articular discomfort.

An attack of gout may occur at any hour, but the tendency is for it to develop during the night. A joint warning sign (an unusual sensation in the joint such as tingling, numbness, or an ache) may herald the onset of an attack of gout by several hours. Close questioning may reveal periarticular desquamation after an acute attack.

An acute attack of gout may occur after any stressful condition. It may be precipitated by direct trauma to the joint masking as a sprain or bruise. Attacks may follow surgical procedures and mimic phlebitis or cellulitis. Acute illnesses such as a heart attack, passage of a urinary stone, or acute hemorrhoids may be followed shortly by an acute attack of gout. Rapid loss of weight or excessive dietary indiscretion may result in acute attacks of gout.

One should suspect the existence of gout in a patient with articular pain and a history of urinary stones, or a strong family history of gout.

From the Department of Internal Medicine, Ochsner Clinic, New Orleans

There is a definite increased incidence of renal stones, hyperuricemia, and gout in families of patients with gout. Some have reported increased association with diabetes mellitus and gout, whereas others have noted no definite correlation.

The mercurial and thiazide diuretics may precipitate attacks of gout. Such injections as liver extracts, insulin, ergotamine tartrate, thiamine hydrochloride, and ACTH have been reported to cause exacerbation of symptoms.

Chronic pain does not rule out a diagnosis of gout. An occasional patient may complain of chronic polyarticular pain without preceding acute attacks. Chronic gouty arthritis may be manifested as chronic pain plus intermittent acute attacks. "Palindromic rheumatism" (acute arthritis of short duration, recurring for several years) may be confused with and suggest acute gout on cursory evaluation. If the serum uric acid is elevated, only further observation may reveal the diagnosis. Degenerative articular disease and occasionally rheumatoid arthritis may dominate the clinical picture, and underlying gouty arthritis may make the problem more difficult to handle and cause atypical or bizarre manifestations.

Thoracic pain of gouty origin, simulating cardiac pain, has been reported.[3] The pain is skeletal, unrelated to exertion, and relieved by administration of colchicine but not the nitrites. The pain is sharp, without extension into the neck or arms, and may last minutes to hours.

VARIATIONS IN SIGNS

The clinician must be alert for objective signs of disease during physical examination of a patient with articular complaints. Objective signs might be synovial thickening, effusion, alteration in articular motion, atrophied muscles, and nodules. Signs such as exudates on funduscopic examination, lymphadenopathy, splenomegaly, and rashes may suggest a systemic disease other than gout.

The physical findings during the acute attack of gout are usually minimal except for acute monarticular arthritis. A small percentage of patients are febrile (up to 102° F.), irritable, and anorexic.

Gout has a predilection for the proximal joint of the great or little toe, whereas in rheumatoid arthritis the second, third, and fourth toes tend to be affected. No peripheral joint is immune to attack but the shoulders and distal joints of the toes and fingers seem to be rarely affected.

Tophi in a patient known to have gout indicate the chronic stage. Such lesions occur classically on the helix or anthelix of the ear. They have been reported in a variety of areas throughout the body, related or unrelated to the joint. The reported incidence of tophi in gout ranges from 21 to 48 per cent of cases. Tophi are found in less than 2 per cent of patients during the initial acute attack. These lesions must be differentiated from rheumatoid nodules, rheumatic fever nodules, and sarcoids. Since tophi are pathognomonic of gout, biopsy of a suspected lesion may be an important adjunctive study in arriving at a definite diagnosis.

Sherman[6] described gouty changes, noting that urate deposits were seen in articular cartilage, marrow, synovial membranes, joint capsules, bursae, ligaments, and tendons. She observed that the deposits provoked an inflammatory reaction of multinucleated foreign body giant cells.

VARIATIONS IN RESULTS OF LABORATORY STUDIES

Elevation of serum uric acid is mandatory for a diagnosis of gout, but such elevation does not necessarily indicate a diagnosis of gout. The first attack of gout may rarely reveal normal or borderline serum uric acid level. Drugs taken by the patient may alter the blood level, masking the true concentration. Serum uric acid concentration may be reduced by large doses of acetylsalicylic acid (4 to 5 gm. daily) bishydroxycoumarin, phenylbutazone, cortisone derivatives, ACTH, probenecid, or sulfinpyrazone. Certain drugs tend to elevate the serum uric acid, such as acetylsalicylic acid (small doses, 1 to 2 gm. daily), thiazide derivatives, and pyrazinamide.

The serum uric acid level tends to be lower in women of menstruating age (up to 5 mg. per 100 ml.) than in men (up to 6 mg. per 100 ml.) using a normal of 6 mg. per 100 ml. The level in women of postmenopausal age tends to be about the same level as in men. At times this factor may be of importance in diagnosis. The incidence of gout in women is about 5 per cent, these being largely in the postmenopausal age.

Serum uric acid levels are usually higher in secondary gout than in primary gout. The level in primary gout is usually above 7 mg. per 100 ml. (using a normal of 6 mg. per 100 ml.), while that of secondary gout ranges from 12 to 14 mg. per 100 ml.

Nonspecific changes occur during the attack, such as leukocytosis and elevation of sedimentation rate, but these values return to normal as the acute attack subsides.

Once gouty changes involve the kidneys, elevation of the blood urea nitrogen and serum creatinine will appear. Early renal involvement may be suggested by proteinuria, a fixed specific gravity, or pyuria.

Analysis of synovial fluid is an important laboratory measurement of gout. Urate crystals may be seen microscopically within leukocytes during an acute attack and extracellularly only during asymptomatic period.

McCarty and associates[9, 10] pointed out the importance of crystal analysis in articular fluid. By means of crystal analysis they showed that calcium pyrophosphate crystals, as well as uric acid crystals, may precipitate acute articular inflammation. Since their report, pseudogout has become a recognized entity which may simulate an acute attack of gout. Uric acid crystals reveal negative birefringence, whereas calcium pyrophosphate crystals reveal weakly positive birefringence, under polarized light.

The effusion of an acute gouty joint will reveal inflammatory changes with decreased viscosity and increased leukocytes, but rarely will the cell count be truly purulent (average count 10,000 to 15,000 cells per cu. mm. with neutrophils predominating). The glucose level in

the articular fluid is usually not altered. One must be constantly alert to the possibility of an acute infection masking as gout.

Tissues being examined for gout should be fixed in absolute alcohol, since the crystals are water-soluble in the routine fixatives.

Roentgenography is an important aspect of evaluation of the joint and may yield valuable information. Radiographic changes are not apparent during the early stages of gout. Juxta-articular demineralization is an unusual finding in early uncomplicated gout and may suggest another cause such as rheumatoid arthritis. Tophi may become calcified and may give an unusual appearance on roentgenograms. Demonstration of calcified articular cartilage in a patient with an acutely inflamed joint should strongly suggest pseudogout. The typical cystic lesions of gout have a bubble-shaped or basket-weave appearance. Cystic lesions of joints may be seen in many other diseases affecting joints.

SYSTEMS AFFECTED BY GOUT

A brief resume of the less common articular and nonarticular manifestation of gout will be presented to emphasize the variability of this disease.

ARTICULAR. In a recent editorial on sacroiliac gout, it was noted that although rare it probably is more common than was first apparent.[2] Sacroiliac involvement seems to occur primarily in patients with chronic gout. Malawista and associates[8] reported characteristic changes of gout in the sacroiliac joints in 7 of 95 patients.

Several cases of gouty arthritis of the hip have been reported. One patient did not respond favorably to colchicine, but the diagnosis was proved on biopsy.[20]

Hall and Selin[6] reported postmortem demonstration of gouty changes in the posterior articulations of several lumbar vertebrae, plus involvement of the capsules, ligaments, and articular cartilages in a 50-year-old man with gout of three years' duration. Tophi have been reported in the intervertebral disks.

Gout rarely affects the central nervous system. Koskoff and coworkers[7] reported a case of a 44-year-old man with tophaceous gout in whom paraplegia developed; at operation a large mass of sodium urate crystals was compressing the spinal cord.

PERIARTICULAR SOFT TISSUE. Gout may involve bursae, tendons, ligaments, and muscles. Golding and Thompson[4] reported five cases of gout with the presenting complaint of tennis elbow. This was 4.6 per cent of a series with this presenting complaint.

A carpal tunnel syndrome may result when tophi involve the transverse carpal ligaments, causing pressure on the median nerve. Ward and associates[19] reported such a case in which considerable fibrosis surrounded the tophi. Because of this finding, they suggested that uricosuric drug therapy may be inadequate and that surgical correction may be necessary for complete recovery.

Nonspecific muscle aching may occur with gout. Pepper and Mann[14] described recurrent aching in the legs of long duration, which they termed irregular gout. This symptom was associated with elevated serum uric acid level and was reported to respond to routine gout therapy. Their patients had no other apparent underlying disease or other evidence of true gout.

RENAL. Renal involvement is the major problem in gout. Although articular involvement is more apparent, renal involvement rises with the chronicity of the disease. Renal involvement may be manifested as nephrosclerosis, gouty nephropathy, pyelonephritis, or a combination of these.

CARDIOVASCULAR. Pengelly[13] referred to the writings of Sir William Osler, who considered pericarditis to be "not an infrequent terminal complication of gout." Paulley and associates[12] reported three cases of benign pericarditis that may have been caused by gout. Moore and Weiss[11] reported association of hyperuricemia and coronary artery disease to be seemingly as common as hypercholesterolemia and coronary disease. There have been several reports of tophi involving valve leaflets, coronary vessels, conducting systems, and interstitial tissue of the myocardium.[15, 18]

EYE. Gouty deposits have been reported in the conjunctiva, cornea, sclera, and iris. Spanopoulous[17] reported a case of gouty iritis which responded favorably and rapidly to colchicine.

SALIVARY GLANDS. Blatt and co-workers[1] reported a case of uric acid calculus of the parotid gland which disappeared with probenecid (Benemid) therapy. Gouty tophi have been reported in the tongue, epiglottis, vocal cords, and arytenoid cartilages. Goobar and associates[5] reported associated parotid enlargement and increased salivary gland uric acid in 41 of 48 patients with primary gout. Blatt and co-workers pointed out that the parotid gland actively excretes uric acid. An acid medium creates a good environment for precipitation of uric acid, thereby posing a potential complication of gout.

SUMMARY

Gout has excited attention and inspired investigators through the ages. Its familiarity may reduce attention to its less obvious manifestations. Clinicians need to maintain a high index of suspicion regarding gout, since it is one of the most treatable diseases involving joints. This paper has endeavored to clarify the unusual manifestations to assist in earlier diagnosis of the disease.

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Extrathoracic Manifestations of Bronchogenic Carcinoma

HURST B. HATCH, JR., M.D.

RONALD J. KNUDSON, M.D.

The experimental manifestations of bronchogenic carcinoma are widely varied and often bizarre. Most of them, however, occur in association with malignant disease of other organs, so that they cannot be considered pathognomonic of bronchogenic carcinoma. Since these manifestations may be the initial clue to the presence of cancer of the lung, instead of the classical symptoms of cough, hemoptysis, and pain in the chest, it is important to be familiar with them if this highly fatal disease is to be diagnosed in its early stages when surgical excision is possible.

Knowles and Smith[4] classified the extrathoracic manifestations of bronchogenic carcinoma into five groups: metabolic, neuromuscular, connective-tissue and osseous, vascular, and hematologic. For purposes of this discussion their excellent classification will be used.

Five hundred and thirty cases of bronchogenic carcinoma encountered at the Ochsner Clinic from 1950 to 1959 were reviewed in an effort to determine the incidence and types of extrapulmonary symptoms in these patients. This series has the usual age and sex distribution for cancer of the lung. There were 474 male and 56 female patients, 417 of whom were between 50 and 89 years of age, and 113 between 30 and 49 years.

This discussion includes all extrathoracic manifestations in the series. In many patients symptoms originated in more than one site. For comparative purposes only the local and metastatic manifestations will be discussed.

Metabolic

The reported metabolic manifestations of bronchogenic carcinoma include Cushing's syndrome, hypercalcemia, excessive production of antidiuretic hormone, and carcinoid syndrome. Reports might suggest that Cushing's syndrome is a common extrapulmonary manifestation

From the Section on Chest Diseases, Ochsner Clinic, New Orleans, Louisiana

Table 1. *Metabolic Extrathoracic Manifestations of Bronchogenic Carcinoma*

MANIFESTATION	CASES
Cushing's syndrome	1
Hypercalcemia	2
Gynecomastia	1
TOTAL	4

of bronchogenic cancer, but we have only one such case in our series (Table 1). The relative infrequency of hypercalcemia (two cases) was surprising, since one might have expected this manifestation to be more common, particularly in patients with involvement of the skeletal system. No patient had excessive excretion of antidiuretic hormone, but since this series was reviewed we have seen two patients with this metabolic defect. One patient had gynecomastia. No patient had the carcinoid syndrome.

In this series there were four metabolic abnormalities. This represents 3.9 per cent of the 101 extrathoracic manifestations in this series.

Neuromuscular

Four neuromuscular abnormalities have been described in patients with bronchogenic carcinoma. The low incidence of these abnormalities in our patients (Table 2) is unusual for such a large series. As in other reported series, corticocerebellar degeneration was the most common in our patients. In patients with corticocerebellar degeneration when first seen, the onset of illness may be rapid with manifestations of loss of cerebellar function, such as ataxia, nystagmus, dysarthria, tremor, and vertigo; occasionally the spinal fluid shows definite abnormalities, such as increased protein and lymphocytosis.

Psychosis is a rare neurologic abnormality associated with bronchogenic carcinoma; only one patient in our series was psychotic. We have noted amelioration of psychotic behavior after surgical treatment of patients with bronchogenic carcinoma, which we believe is unrelated to

Table 2. *Neuromuscular Extrathoracic Manifestations of Bronchogenic Carcinoma*

MANIFESTATION	CASES
Cortical cerebellar degeneration	6
Peripheral neuropathy	4
Myopathy or polymyositis	3
Psychosis	1
TOTAL	14

the stress imposed by the operation or to analgesics. Other neuromuscular abnormalities noted in this series were neuropathy and carcinomatous myopathy or polymyositis.

Connective-Tissue and Osseous

As would be expected, clubbing with and without osteoarthropathy is common in patients with bronchogenic carcinoma. Almost twice as many of our patients had clubbing as had osteoarthropathy or periosteitis (Table 3). Periosteitis without clubbing is most unusual.

Table 3. *Connective-Tissue and Osseous Extrathoracic Manifestations of Bronchogenic Carcinoma*

MANIFESTATION	CASES
Clubbing	52
Osteoarthropathy	23
Acanthosis nigricans	1
TOTAL	76

The pathogenesis of these connective-tissue abnormalities, as is true of most extrathoracic manifestations of carcinoma, has never been adequately explained, although many pathogenetic vascular and neural theories have been offered.[3] It is interesting that after removal of the tumor or vagotomy, the clubbing will gradually disappear and the pain of the osteoarthropathy will improve.[2]

Acanthosis nigricans was present in only one of our patients. It has been stated that this cutaneous abnormality precedes appearance of cancer in 20 per cent of patients, and that cancer will eventually develop in any patient who has this condition when first seen, if it is not there at the time of the diagnosis of acanthosis nigricans.[1] On admission none of our patients had dermatomyositis or scleroderma, both of which have been reported as extrapulmonary manifestations of bronchogenic carcinoma.

Vascular (Endothelial)

Thrombophlebitis is a manifestation of some patients with bronchogenic carcinoma. In seven of our patients migratory thrombophlebitis was present on admission to the hospital. None of our patients had nonbacterial thrombotic endocarditis. We consider thrombophlebitis as a suspicious sign of cancer, and we make a thorough study of every patient with phlebitis in the age group in which cancer is most common.

Hematologic

The only hematologic manifestations in patients with bronchogenic carcinoma are anemia, fibrinolytic purpura, and cryofibrinogene-

mia. One hundred and fifty-nine of our patients were anemic when first seen, but none had either of the other two manifestations. Since definitive studies were not undertaken, the different types of anemia were not determined, but they included hemolytic, myelophthisic, and hemorrhagic anemia. It is recognized, of course, that chronic anemia is characteristic of all wasting diseases. Decreased erythrocytic survival and impaired bone marrow function of unknown cause sometimes will be found in these patients.

CONCLUSION

This brief review of the extrathoracic manifestations encountered in 530 patients with bronchogenic carcinoma indicates that the classical triad of cough, hemoptysis, and pain in the chest is not necessarily the only presenting complaint of patients with bronchogenic carcinoma. Among the 530 patients, 79 (about 15 per cent) had extrathoracic manifestations (exclusive of anemia) on admission; these 79 patients had a total of 101 extrathoracic manifestations (exclusive of anemia). These were metabolic, neuromuscular, connective-tissue and osseous, vascular, and hematologic. Realization that these rarer symptoms and signs may be the initial evidence of this dreaded disease may result in earlier diagnosis when surgical excision is feasible.

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Unusual Manifestations of Diffuse Obstructive Emphysema

JOSEPH K. BRADFORD, M.D.

A single specific cause of diffuse obstructive emphysema, or destructive emphysema, as it has been called by some, is unknown. Important contributory factors, such as cigarette smoking, asthma, air pollution, and generalized pulmonary diseases, are usually discernible in the patient's history. Many persons with a history of one or more of these factors do not get emphysema. The part played by aging is uncertain.

The patient with well developed emphysema is easily recognizable. He has difficulty in breathing, ranging from breathlessness when walking rapidly to labored breathing when sitting or standing, most of the day leaning forward, unable to walk at all. The anteroposterior diameter of the thorax is increased. The thorax may be fixed, and the patient may be using his cervical muscles in breathing. Cough and expectoration may be minimal or extremely bothersome. Wheezing occurs most often after the patient arises in the morning. Dependent edema is present with complicating congestive heart failure. A plethoric appearance with cyanosis of the nail beds is common if pulmonary hypertension is present. These patients demonstrate varying degrees of anxiety, tension, depression, and discouragement. Weakness, particularly of the legs, may be a major complaint.

On examination, the breath sounds are generally distant to varying degrees. There are variations in different portions of the lungs. Expiration is prolonged. Although wheezing may not be evident during quiet breathing, it can often be heard at the end of forced expiration. Persistent post-tussive rales are not characteristic of emphysema. The cervical veins may be distended and the liver tender in early congestive failure.

Roentgenograms of the chest, properly made, demonstrate dark pulmonary fields. The vascular markings at the periphery are diminished or absent. The retrosternal space is increased in the lateral projection. The diaphragm is flattened. The heart is often extremely small.

Measurement of the vital capacity shows varying degrees of reduc-

From the Section on Chest Diseases, Ochsner Clinic, New Orleans, Louisiana

tion. This measurement may be used as a rough estimate, in the absence of other pulmonary disease, of the loss of elasticity or compliance of the lungs.

Although there may be disagreement by some, it seems fair to state that (1) the patient who will get diffuse obstructive emphysema can be recognized early and the irreversible structural changes in the lungs prevented to some extent; (2) almost every patient with symptoms due to emphysema can be made more comfortable and often rehabilitated to a striking degree; and (3) there is no inevitability about progression of the permanent pulmonary changes. Deaths attributed to emphysema can at times be prevented, or at least deferred. In support of these statements, it is well to remember that at necropsy a surprising amount of normal pulmonary tissue is found scattered throughout severely overdistended lungs.

Knowledge of some of the less common, but practical, clinical and laboratory abnormalities may be important in the proper evaluation and long-term management of patients with pulmonary insufficiency due to emphysema. In addition, infinite patience, encouragement, and frequent observation are equally as important.

CLINICAL MANIFESTATIONS

1. Adequate measures to drain the bronchi, including increased fluid intake, use of bronchodilator drugs and expectorants, and postural drainage should eliminate persistent post-tussive rales. If these sounds are heard constantly in a localized section of the lung, it is likely that there is some other structural alteration of the lung, such as bronchiectasis. Such a change may alter the therapeutic regimen and prognosis.

2. Peptic ulcer occurs more often in patients with emphysema than in the general male population. Gastrointestinal bleeding, therefore, can complicate the clinical picture, and may explain normal hemoglobin and hematocrit values in a patient with emphysema and pulmonary hypertension who would be expected to have elevated values. Symptoms of shock, which can occur for other reasons in patients with severe emphysema, can be due to unrecognized gastrointestinal bleeding.

3. Some patients who complain of dyspnea on exertion have minimal abnormal physical signs. The breath sounds may be normal. The vital capacity determination in the office may indicate the predicted value, or one even higher. If the element of time is added to the determination, however, with the use of a timed vitalometer, or the determination of maximum breathing capacity, definite obstruction to the outflow of air will be apparent. This abnormality, in itself, does not mean emphysema. The patient does need treatment, however, to prevent permanent structural changes in the alveoli.

4. Some patients with incapacitating pulmonary insufficiency are content to spend most of the 24 hours sitting in one position, leaning forward with arms on the upper legs. One of the reasons given for this is that when they attempt to walk, their legs are "too weak." Hypoxia

and electrolyte imbalance do contribute to weakness. Disuse atrophy of the quadriceps muscles, however, can be the major cause of failure of these patients to use their legs in walking. If so, physical therapy must become part of the therapeutic program.

5. Patients with advanced obstructive emphysema and pulmonary hypertension may complain of awakening in the early morning hours with severe headache, usually frontal. This symptom is an indication of severe hypoxia and is of serious prognostic import.

6. A change in mental acuity, somnolence, semicomatose states, and coma, with or without evidence of shock, are the most serious indications of impending disaster in severe emphysema. Information obtained from members of the family may give the first clue. Patients with these manifestations who have emphysema may not have CO_2 narcosis, but it is imperative to prove that severe respiratory acidosis is not present. Evidence of increased cerebrospinal fluid pressure, such as clouding of the optic discs, can be demonstrated at times. Initial determination of arterial pH, oxygen tension, carbon dioxide tension, and oxygen saturation, along with current values for sodium, potassium, and chloride, are imperative to evaluate these neurologic symptoms. Dulfano and Ishikawa[1] reviewed this subject in detail.

LABORATORY MANIFESTATIONS

Diffuse obstructive pulmonary disease is a steadily increasing problem. The word "emphysema" has a frightening connotation to many. Its use may precipitate emotional crises, insurance problems, forced retirement from remunerative work, and legal battles for compensation and disability. It bears repeating that all patients exhibiting obstruction to the outflow of air do not necessarily have emphysema.

A number of uncomplicated, relatively inexpensive laboratory devices can be used in the office to classify the disease more accurately, determine which patients need more detailed studies in a pulmonary laboratory, and follow the patient's progress more accurately. At least one hospital in every community should have facilities for determining the pH and the partial pressures of carbon dioxide and oxygen in arterial blood. This technique is the most accurate. It is not difficult to acquire proficiency in arterial puncture.

Well equipped and well staffed pulmonary physiology laboratories are available, at least regionally, and should be used for adequate initial evaluation of symptomatic patients and application of proper therapeutic programs. A physician well trained in the application of all available knowledge in the management of emphysema with its possible serious complications is more valuable than any amount of laboratory study.

All components of a hospital-laboratory complex may be brought into use in the evaluation and treatment of patients with emphysema.

Roentgenographic Aspects. Postero-anterior projections of the lung alone may be misleading in evaluation of obstructive pulmonary

disease. A lateral view should always be included. In addition, films made during maximum inspiration and expiration may indicate that suspected loss of elasticity is more apparent than real. Prompt, adequate excursion of the diaphragm can be demonstrated. This can be used as a rough guide to evaluate the effectiveness of treatment. In addition, with these two views, the degree of air trapping and its location become apparent.

Bullous changes in the lungs do not necessarily mean impairment of ventilatory ability. Increasing size of these areas, especially if accompanied by evidence of compression of adjacent pulmonary tissue, may indicate a patient whose breathing could be improved by surgical excision of the nonfunctioning bullae. Serial observation of the size of the major pulmonary arteries can indicate development of pulmonary hypertension and presage congestive heart failure.

HEMATOLOGIC ASPECTS. Patients with pulmonary insufficiency may have presenting symptoms consistent, in part, with a diagnosis of polycythemia vera. More often, however, elevated hemoglobin and hematocrit values are found at the time of initial examination. It is wise to determine whole blood and plasma volumes before a decision is made with regard to both the cause and the possible advisability of phlebotomy.

The personality of patients with emphysema is often such that stress erythrocytosis is common. This condition would not require the same management as true polycythemia or secondary polycythemia.

Phlebotomy is valuable to decrease venous return to an overloaded right ventricle. The amount and frequency of venesection should be determined by accurate laboratory studies.

BACTERIOLOGIC ASPECTS. Infection of the upper respiratory tract is probably the most important single factor in precipitating an acute crisis in a patient with severe emphysema. The causative organism must be identified promptly and sensitivity studies done so that proper antimicrobial therapy can be instituted early.

Organisms from the mouth and nasopharynx are included if the patient is asked to expectorate. These may not be the true pathogen responsible for severe bronchitis or pneumonia. It is important, therefore, to depend on a specimen obtained by a deep cough. Use of expectorant medications, increased fluid intake, and inhalation of simple hypertonic solutions, such as 3 per cent sodium chloride containing 10 per cent ethylene glycol, aid in getting an adequate sputum specimen. These are also therapeutic measures for proper cleansing of the airways.

Inspection of a patient's sputum gives much information concerning the effectiveness of treatment. The bacterial flora does change with treatment, however, and repeated cultures, in long-term treatment programs, are desirable. If infection does not resolve with specific treatment, the sputum may be examined for the presence of anaerobic organisms, fungi, and acid-fast bacilli.

Regular use of antimicrobial drugs has been advocated as prophylactic treatment of emphysema. Such treatment is often given from seven to ten consecutive days each month. Periodic sputum cultures

would be helpful in determining the proper drug to be used in such a program. Patients who demonstrate pneumonic processes with considerable fever should have serial blood cultures.

Chemical Aspects. The electrolyte values in emphysematous patients with serious infection, cardiac decompensation, or respiratory acidosis may be of vital importance. For example, metabolic alkalosis due to hypochloremia, hypokalemia, or both, is common, and proper control is imperative. Frequent determinations serve to guide the physician in prescribing the amount and duration of potassium chloride therapy.

These patients may have diseases of other body systems, or may have been taking medications which disturb the acid base balance in other ways. This imbalance is a serious handicap in the treatment of cardiac decompensation or respiratory acidosis.

Pulmonary Physiology. The importance of knowing the partial pressures of carbon dioxide and oxygen and the pH of arterial blood has been emphasized. Effective treatment depends on knowing the degree of hypoxia and the severity of the respiratory acidosis. A pH of less than 7.25, oxygen tension less than 50 mm. of mercury, and carbon dioxide tensions greater than 60 mm. of mercury are considered to be critical levels. These values dictate the advisability or inadvisability of assisted ventilation and the type which should be used. The duration of assisted ventilation depends entirely on attaining satisfactory blood gas values.

The most rapid way to overcome hypoxia is by use of oxygen. Indiscriminate use of oxygen, however, may prove fatal, and frequent monitoring of arterial blood gases is the only safe method for determining proper use of oxygen. In seriously ill patients, or in poor risk patients who require surgical treatment, monitoring of blood gas values several times during an operation, and for several days thereafter, may be lifesaving.

Biophysical Aspects. Scanning of the lung after intravenous injection of proper materials is an acceptable method of determining regional blood flow within the lungs. It may be of particular value in patients with emphysema in whom resection of the lung is being considered. Techniques for lung scanning in which inhaled material is used are still in the developmental stage.

SUMMARY

There is much that is unknown about emphysema, particularly as regards fundamental cause and progress of the disease in a given patient. We do have information and laboratory methods which, if used properly, will enable physicians to recognize diffuse obstructive pulmonary disease early in its course, to prevent its progression, to assist in rehabilitation of many patients, and to treat the seriously ill patient.

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Variants of Acute Leukemia

DON M. SAMPLES, M.D.

The clinical and laboratory manifestations of acute leukemia are so numerous that the briefest discussion of those occurring in less than 25 per cent of patients would require more than the allotted space and would be repetitious of other reports.[5, 9] This discussion will deal with variants which, though unusual, are being recognized with increasing frequency.

PRELEUKEMIC ACUTE LEUKEMIA

Leukemia usually is not difficult to diagnose. In some patients, however, a variety of hematologic abnormalities may be present for some time before the diagnosis of leukemia is made. Block and associates[4] termed this preceding state "preleukemic acute leukemia" when they reported 12 cases of patients whom they had observed for as long as 27 months before acute myelogenous or stem-cell leukemia developed. Increasing numbers of such cases are being recognized.

The preliminary phase is characterized by anemia, neutropenia, thrombocytopenia, or a combination of these. The anemia usually is manifested as "refractory anemia," often accompanied by erythroid hyperplasia in the bone marrow and normal or reduced reticulocytes. Less common is Coombs-negative hemolytic anemia with increased reticulocytes and elevated serum bilirubin level. In others, elevated excretion of fecal urobilinogen has been demonstrated with a high hemolytic index but normal or low reticulocyte counts. Decreased erythropoiesis has been documented by ferrokinetic studies in some. Nucleated red blood cells are at times observed in the peripheral blood, but this has not correlated well with bone marrow erythroblastosis. Rarely, the bone marrow has shown distinct megaloblastic arrest, closely resembling that of pernicious anemia but unresponsive to vitamin B_{12} or folic acid.

Neutropenia has been present in most patients, and infection a problem in many. Changes in the bone marrow are inconsistent, ranging from hypoplasia to distinct hyperplasia of the granulocytic series with

From the Section on Hematology, Ochsner Clinic, New Orleans, Louisiana

some evidence of maturation arrest—changes which suggest toxic agranulocytosis on the one hand and "splenic neutropenia" on the other. Similarly, the thrombocytopenia has been accompanied by considerably reduced numbers of megakaryocytes suggestive of toxic depression, or plentiful megakaryocytes in keeping with idiopathic thrombocytopenic purpura. The bone marrow in those patients with pancytopenia has been truly hypoplastic in a few, and the diagnosis of "aplastic anemia" quite appropriate. Most patients had erythroid hyperplasia with hypoplasia or hyperplasia of the granulocytic series, and normal to increased numbers of megakaryocytes. No evidence of leukemia can be found in the marrow during this time.

Lymphadenopathy is not prominent and usually the liver and spleen are not palpable until the definite onset of leukemia. Spleens removed during this prelude have shown no evidence of leukemia. They have been described as normal or hyperemic, or as showing hyperplasia of the lymphoid follicles and hemosiderosis. Likewise, changes in the liver have not been impressive and have not suggested a diagnosis of leukemia. During this period the illness usually is relatively benign, though unresponsive to administration of iron, cobalt, vitamin B_{12}, liver, adrenal corticoids, androgens, and various other agents. In patients with hemolytic anemia, splenectomy has provided temporary benefit at best.

The hematologic abnormalities may be present from a few months to a few years (nine years in one instance) before the onset of recognizable leukemia. Peripheral monocytosis often precedes the appearance of lymphadenopathy, hepatosplenomegaly, and the ultimate recognition of leukemia. During this time increased marrow hyperplasia and immaturity of the granulocytic series are noted with progression shortly to a frankly leukemic picture. The rapidity with which leukemia may develop is emphasized by Block's report in which 9 of his 12 patients had no diagnostic changes in the marrow until less than two months before death; one of these had aplastic marrow with a few areas of regeneration only 16 days before death, but on the day of death the marrow was clearly indicative of acute leukemia. With few exceptions, the course of the leukemic phase has been unusually brief and unresponsive to therapy. Most cases terminate as acute myelocytic or "stem-cell" leukemia, but many cases of acute monocytic leukemia have been observed, and 9 of 22 cases of "chronic" monocytic leukemia were preceded by a preleukemic phase.[21]

Preleukemic acute leukemia is a diagnosis made in retrospect. At present it cannot be distinguished from other aplastic or refractory anemias. The obvious question, is leukemia responsible for the entire illness, or does the preceding illness predispose to the development of leukemia, cannot be answered. In potentially leukemic disorders, prospective studies of chromosomal abnormalities which are similar to those found in leukemia may give some answers.[18]

Certain hematologic syndromes have a propensity to terminate in leukemia. The classification by Rowley and associates[18] seems appropriate: aplastic, myelodysplastic, and myeloproliferative. ". . . the myelodysplasias refer to a group of disorders exhibiting morphologic

evidence in the marrow and the blood of disturbed formation of any, or any combination, of the major blood cell lineages (erythroid, granulocytic, megakaryocytic), not characteristic of the aplastic, the myeloproliferative, or the leukemic states, yet displaying certain features often intermediate or transitional between these conditions." In the myelodysplasias they included refractory hyperplastic anemia, sideroachrestic anemia, atypical myeloid disorder, preleukemic acute leukemia and primary splenic hematopenia.

SMOLDERING ACUTE LEUKEMIA

The course of untreated acute leukemia is brief; the median survival of children is 2.7 months.[21] With treatment, this median survival is extended to 12 to 14 months. This increase is related to the frequency and duration of induced remissions, which depend largely on the type of leukemia.

Rheingold and associates[16] called attention to an atypical variety of acute leukemia which has a more prolonged and often more benign course even without specific antileukemic therapy. They called it smoldering acute leukemia. It resembles preleukemic acute leukemia in a number of aspects. The onset is insidious. Anemia or, less often, thrombocytopenia or leukopenia, precedes the diagnosis by even a few years. The clinical picture is mild with few systemic manifestations such as fever, night sweats, anorexia and loss of weight. The physical findings usually are limited to pallor, purpura, or both; the lymph nodes, liver, and spleen are not significantly enlarged. Early, the peripheral blood does not show blasts, and the differential count generally is normal.

In preleukemic acute leukemia the bone marrow is not diagnostic of leukemia during the prodromal phase, and the diagnosis is made in retrospect. In contrast, the bone marrow in smoldering acute leukemia is diagnostic of acute leukemia when the patient is first seen. Blasts are present in variable numbers, many are "wild" looking young cells with prominent nucleoli; there may be striking preservation of nucleated red cells and megakaryocytes to the extent that the increase in blast cells may be overlooked. The red cell precursors are often large and megaloblastoid. Rheingold and associates stressed the importance of correlating the marrow with the clinical picture to exclude the various causes of leukemoid reactions. These adult patients survived from eight months to three years (average more than one year) without specific therapy. Unless the leukemia became rapidly progressive, they were given transfusions for anemia, antibiotics for infection, and adrenal corticoids for hemolysis or thrombocytopenia with bleeding.

The patients of Rheingold and co-workers had acute myelocytic leukemia. Some of the cases of "chronic monocytic leukemia" of Sinn and Dick[21] had a smoldering course and bone marrow morphologically compatible with a diagnosis of acute leukemia.

Though early diagnosis may have made the period of smoldering appear longer and more benign, these patients do seem to have an

atypical variant of acute leukemia. Thus, the course of acute leukemia is not always fulminant and short.

Equally unusual are the 71 patients with acute leukemia who survived from 5 to 12 years after the diagnosis was made.[6] Thirty-six of 53 children and 6 of 18 adults were reported living and well with no evidence of leukemia more than five years after the diagnosis was made. All patients were treated but at least two patients received treatment only during the first year of their disease and were apparently well 12 years later. The explanation for these long survivals and for the smoldering character of some cases of leukemia remains unknown.

ACUTE PROMYELOCYTIC LEUKEMIA

Hemorrhage is a common manifestation of acute and chronic leukemia. It is the chief cause of death in acute myelocytic leukemia. Severe thrombocytopenia is an obvious feature in most patients. Occasionally, the cause is more obscure and other mechanisms have been suggested: qualitative platelet defects, vascular endothelial damage from anoxia or lysins, leukemic infiltration of vessel walls, or circulating anticoagulants.[2]

The role of fibrinolysis in the hemorrhagic diathesis of leukemia has been emphasized recently by Girolami and Cliffton.[13] Hyperfibrinolysis was demonstrated by the euglobulin method in 36 per cent of their patients with acute leukemia, and 25 per cent of those with chronic leukemia. Increased fibrinolytic activity was found in 42 per cent of the patients with hemorrhagic manifestations and in 21 per cent of those who had no apparent bleeding tendency. No significant proteolytic activity was demonstrated in any patient studied. The fibrinogen levels were not recorded nor did they state whether any of their patients had a preponderance of atypical promyelocytes.

Acute promyelocytic leukemia (APL) is a distinct entity characterized by a predominance of atypical promyelocytes, hypofibrinogenemia, and almost invariably a rapidly fatal and hemorrhagic course with poor response to any form of therapy.

Croizat and Favre-Gilly[7] have been credited with reporting the first case in 1949. Though few cases had been reported during the next ten years, the incidence is probably higher than recognized; Rosenthal[17] accumulated 17 cases during a nine year period, and Bernard and coworkers[3] reported that APL represented 6.8 per cent of the 497 cases of acute leukemia seen at the Research Institute for Blood Diseases in Paris.

APL occurs primarily in older children and adults (13 to 82 years) and shows no predilection for sex. Early symptoms consist predominantly of bleeding manifestations: purpura, hematomas, epistaxis, and gingival bleeding. With rare exception the cause of death has been cerebral hemorrhage or, less frequently, gastrointestinal hemorrhage.

The peripheral blood counts show no consistent pattern with the white cell count, hemoglobin, and platelet levels occurring in the same

ranges as in other kinds of acute leukemia. Enlargement of the lymph nodes, liver, and spleen, however, is much less common.

APL is clinically indistinguishable from the more common forms of acute leukemia, though the hemorrhagic manifestations are more severe. Promyelocyte and the fibrinogen abnormalities permit differentiation. The characteristic cell is an atypical promyelocyte. There is asynchronous nuclear-cytoplasmic maturation with an immature and blastic nucleus, sometimes containing nucleoli. The cytoplasm is abundant and relatively mature with little basophilia and contains great numbers of large granules which may completely cover the nucleus. The granules vary considerably in size, shape, and staining characteristics, though most are azurophilic. Auer bodies may be present and unusually large. These abnormal cells predominate in the bone marrow but may be absent from the peripheral blood.

Fibrinogen deficiency is highly characteristic of APL but rare in other forms of leukemia. The mechanism for this deficiency is not clear. Increased fibrinolytic activity has been reported by several authors but, as pointed out by Didisheim and co-workers,[10] the evidence for this consisted solely of rapid disappearance of the clot in all but two cases. The clots are fragile and may disintegrate almost completely with repeated tilting of the tube to check for lysis. The clot will retract to a very tiny clot even in the presence of thrombocytopenia, but it can be detected by careful inspection of the clotting tube contents.

Nilsson and associates[15] demonstrated definite lysis in one case of APL and controlled the hemorrhages by large doses of ϵ-aminocaproic acid, a known inhibitor of fibrinolysin activator. This drug has not been effective in other instances.

In the absence of demonstrable fibrinolysis, most evidence suggests that use of fibrinogen is increased (intravascular coagulation) in that infused fibrinogen rapidly disappears,[10] and the level of circulating fibrinogen is not raised significantly.[17] Also in support of intravascular coagulation, Baker and associates[2] demonstrated a rise in fibrinogen levels and cessation of bleeding when heparin was given intravenously. A second attempt was unsuccessful and administration of heparin was discontinued; at postmortem examination multiple intravascular fibrin thrombi were found.

In addition to hypofibrinogenemia, factor V deficiency has been demonstrated in 10 of 11 patients studied.[10] Though frequently present in APL, factor V deficiency is less specific, for it has been demonstrated in other kinds of leukemia.

The course of APL is characteristically brief, but five patients responded to antileukemic therapy with survival from eight to 24 months. During periods of remission the fibrinogen levels rose, only to fall again with relapse.

ERYTHROLEUKEMIA (DiGUGLIELMO SYNDROME)

"The group of morbid conditions to which the name of Giovanni DiGuglielmo has been attached forms the subject of the most confused

chapter in modern hematology" wrote Dameshek and Gunz.[9] In this section no attempt will be made to clarify the confusion; our knowledge to date will merely be summarized.

In 1917 DiGuglielmo[11] described a mixed erythroblastic-myeloblastic proliferation which he called "erythroleukemia." In 1923 he[11] described a "pure" erythroid proliferation and defined this "erythremic myelosis" as "an autonomous pathologic entity, that is, a primary and specific disease characterized by generalized proliferation of the erythropoietic cells of the bone marrow, analogous to the leukocyte proliferation in leukemia." Thus began the confusion and it mounted as other cases were reported and the spectrum of the disease expanded.

In one of his last papers, DiGuglielmo[12] considered it as one of the "myeloproliferative syndromes" and accordingly recognized a variety of forms: (1) pure: erythremic disease (erythremic myelosis), (2) mixed: erythroleukemia, and (3) polyphasic: passage from one form to another (erythremia to erythroleukemia, to leukemia and, very rarely, vice versa).

Cases of pure acute erythremic disease (erythremic myelosis) are rare. Nonetheless, DiGuglielmo was wont to classify them as: (1) pseudopernicious anemia type with hyperchromic macronormoblastic anemia, (2) pseudoerythroblastomatous type with pronounced polypoidism and gigantism of the erythroblast, (3) pseudoneoplastic type with macroscopic nodules formed by erythroblastic infiltration without the characteristics of a tumor, (4) erythremic or hypoerythremic type, and (5) a type with an initial aplastic phase in the marrow, followed by a hyperplastic phase. This classification is artificially intricate, and overlapping is characteristic. The bone marrow shows preponderant erythroblastic proliferation with arrested maturation of the erythroblasts, as well as bizarre megaloblastoid forms with polypoidism and gigantism. This phase may be acute and fulminating with fever, prominent hemorrhagic manifestations and hepatosplenomegaly terminating within a few weeks. There is severe anemia, the red blood cells showing severe anisocytosis and poikilocytosis. Nucleated red cells are usually numerous, and primitive abnormal forms are common. The reticulocyte count is variable, as is the total white blood cell count. A few myeloblasts may be present (DiGuglielmo thought this was a secondary phenomenon caused by the excessive erythroid proliferation in the marrow with the passage of myeloblasts from the spleen, rather than a leukemic manifestation).

Dameshek and Baldini[8] were impressed by the polyphasic aspect of erythremic disease and called it the DiGuglielmo syndrome. According to this concept, the disease, if it runs its full course, passes through three phases: erythremic myelosis, erythroleukemia, and acute myeloblastic leukemia.

As noted, the first phase is rarely seen in "pure" form. Dameshek and Gunz[9] noted that, even in this stage, a few myeloblasts may be in the peripheral blood, together with foci of myeloblastic proliferation in the marrow. If the patient survives, there is progressive increase in the myeloblastic proliferation, and the disease is then considered erythro-

leukemia. Most patients probably come under observation during the erythroleukemia phase. In this group the age range is wide (11 to 85 years), and males predominate (2:1). The duration of illness after diagnosis is a few months, though occasional patients will survive for a few years. The symptoms are predominantly those of anemia, but in some patients abdominal pain has been prominent early in the course. Purpura and hepatosplenomegaly occur in about one third of the patients; fever and lymphadenopathy are less common.

The anemia and red blood cell changes are similar to those described in erythremic myelosis, though fewer patients have nucleated erythrocytes in the peripheral blood. Circulating myeoblasts are present in most (up to 50 per cent of the white blood cells), and thrombocytopenia is the rule.

The bone marrow shows the erythroblastic changes previously described but there is considerable variation from patient to patient, and there is concomitant myeloblastic hyperplasia. Auer bodies are seen in some instances.

Response to therapy with antileukemic agents is disappointing. Progressive increase in immaturity of the erythroid cells, as well as increase in immature myeloid elements and blast cells, has been described, despite decreasing marrow cellularity with 6-mercaptopurine therapy.[20]

The terminal marrows, probably altered by therapy, show variable pleomorphic and polymorphic hyperplasia with anaplastic erythroid cells, stem cells, "anaplastic blasts," and cells with "histioblastic and hemocytoblastic" character. Often there is considerable individual variability, and pleomorphism is unlike the monotonous morphology observed in most acute leukemia.[20]

Many patients do not survive the erythroleukemic phase. In the few patients surviving this phase the terminal stage is similar to that of acute myeloblastic leukemia.

It has been stressed that the diagnosis may be difficult to make and that the patient must be observed sufficiently long to exclude the diagnoses of hemolytic anemia, myelocytic leukemia, myelofibrosis, pernicious anemia, lymphomas and other neoplasms.

Baldini and associates[1] studied the anemia of the DiGuglielmo syndrome extensively and demonstrated somewhat shortened red cell survival time in most patients. They believed this was due to an intracorpuscular defect of the red cells. There was a great increase in fecal excretion of urobilinogen which, when compared with the relatively minor shortening of red blood cell survival time, suggested heme pigment diversion or increased destruction of precursor red cells in some of the patients. They concluded that there was ineffective erythropoiesis in view of the great increase in marrow erythroid cells and increased iron turnover compared with only slightly increased red blood cell destruction and utilization of iron.

Various relationships of the DiGuglielmo syndrome to vitamin B_{12} or folic acid deficiency and pernicious anemia have been subject of speculation. The possibility that the myeloblasts are atypical pro-

erythroblasts was raised by demonstration of periodic acid Schiff (PAS) staining material in the myeloblast and abnormal erythroblast in this disease, as contrasted with the lack of such staining characteristics in other leukemic myeloblasts and in normal pro-erythrocytes.[15]

The DiGuglielmo syndrome remains confusing. Whether it is truly a leukemia of red blood cells or a corporate finding in myeloblastic leukemia cannot be definitely settled at present. Schwartz and Critchlow[19] realistically concluded: "All evaluation is necessarily offered with the reservations that must be held regarding a rare disease of unknown etiology."

SUMMARY

The clinical manifestations of acute leukemia are numerous, but none is pathognomonic. The various signs and symptoms are related to the very nature of the disease: proliferation and infiltration.

Proliferation of the leukemic cells in the bone marrow may produce anemia, thrombocytopenia, and impaired production of normally functioning leukocytes. Anemia, hemorrhage (into any tissue or from mucous membranes), or increased susceptibility to infection may be the predominant symptom.

Infiltration and proliferation of the leukemic cells in the various tissues and organs produce signs and symptoms as structure or function is altered. The constitutional symptoms, such as fever, fatigue, and irritability, are less well understood and need not be related to cytopenia or infiltration.

Acute leukemia does have a few specific laboratory manifestations. The finding of immature leukocytes in the peripheral blood is important but not pathognomonic of leukemia. Replacement of normal bone marrow elements by sheets of very immature cells (blasts or "pros," for example, promyelocytes, prolymphocytes, or promonocytes) is the most important diagnostic criterion of acute leukemia. Similarly, a diagnosis may be made if foci of these immature cells are found in specimens of the liver and spleen.

Four variants of acute leukemia have been discussed: (1) preleukemic acute leukemia, in which a hematologic illness may precede the overt appearance of acute leukemia for months or years; (2) smoldering acute leukemia, which may have an unusually long and benign course, though the diagnosis is apparent; (3) acute promyelocytic leukemia, in which atypical promyelocytes predominate in the bone marrow and characteristically hypofibrinogenemia contributes to the hemorrhagic diathesis, with frequent decrease in factor V levels also; and (4) erythroleukemia, or the DiGuglielmo syndrome, a confusing disorder which may have three phases: (*a*) acute erythremia or erythremic myelosis in which malignant-appearing erythroid proliferation predominates; (*b*) erythroleukemia in which both erythroblastic and myeloblastic proliferation are prominent; and (*c*) acute myelocytic leukemia. The DiGuglielmo syndrome may terminate in either of the first two phases, or progress to rather typical acute myelocytic leukemia.

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Fibrinolysis: An Unusual Cause of Bleeding

GEORGE H. PORTER, III, M.D.

Many physicians experience discomfiture when confronted by a patient with a "bleeding disorder," for the spectrum of individual causes is broad and the details of some of them are complex. This review discusses the role of *pathologic fibrinolysis* as one cause of hemorrhage. An awareness of the possible role of this interesting process in all patients with abnormal bleeding is essential to correct diagnosis and successful treatment.

Blood coagulation *in vivo* is among the most dynamic of biologic processes: the formation and dissolution of clots maintains the blood fluid and the circulation patent. Plasma not only has the capacity to form fibrin, but a fibrinolytic system normally exists for its dissolution and liquefaction.[25, 51, 55] Excessive or pathologic activation of the normal physiologic process of fibrinolysis may be associated with severe hemorrhage.

PHYSIOLOGY OF FIBRINOLYSIS

The breakdown of fibrin (fibrinolysis) is achieved by the action of fibrinolysin (plasmin), a proteolytic enzyme which exists in normal plasma as an inert precursor, profibrinolysin (plasminogen). Plasmin is capable of digesting not only fibrin but also other coagulation factors: fibrinogen (Factor I), proaccelerin (Factor V),[23] antihemophilic globulin (Factor VIII), prothrombin (Factor III), Christmas factor (Factor IX or Plasma Thromboplastin Component). Other proteins known to be degraded by the action of fibrinolysin are adrenocorticotropic hormone (ACTH), growth hormone, gamma globulin, and the first component of complement.[32, 40]

With fibrinolysis, the plasma *may* contain appreciable amounts of fibrinogen, but the fibrinogen level is often diminished when the process is severe, since fibrinogen is also digested by fibrinolysin. When the titer of circulating fibrinolysin is high, blood is either incoagulable or clotting delayed. If a clot does form, it rapidly lyses.

From the Section on Hematology, Ochsner Clinic, New Orleans, Louisiana

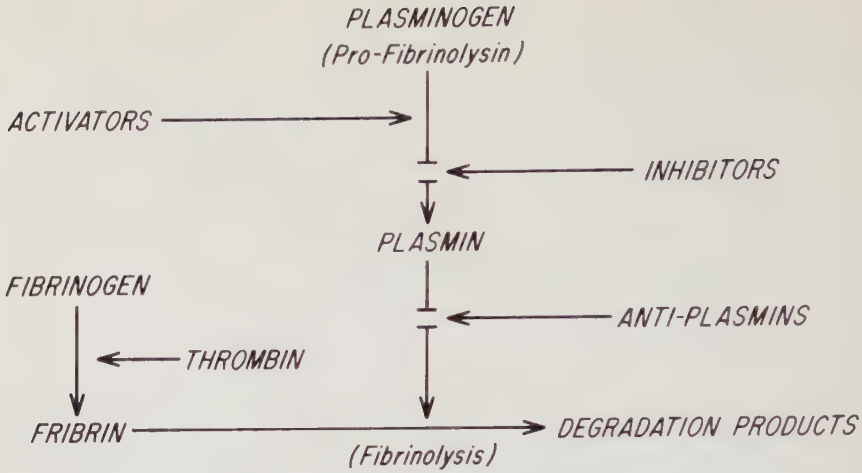

Figure 1. A simplified scheme of fibrinolysis.

Fibrinolysin is capable, under proper circumstances, of altering the precursors of plasma kinins to produce biologically active polypeptides which increase permeability of the blood vessels and contract smooth muscle. Profibrinolysin (plasminogen), the inactive precursor, is probably made in the liver.[7] Its conversion to fibrinolysin (plasmin) can occur either in plasma or within the strands of a clot.[31] When plasmin is present in appropriate amounts, the linkages holding fibrin monomers together are split, and clot lysis occurs.[48] A greatly simplified scheme of fibrinolysis is presented in Figure 1.

It should be remembered that the end-products of fibrin digestion may contribute to the bleeding tendency; powerful anticoagulants are released from the degradation of fibrin by fibrinolysin.[16]

Activation of Fibrinolysis

Considerable attention has been given to the mechanism of plasminogen activation.[35] Naturally-occurring activators include the tissue and plasma kinases, urinary activator (urokinase), trypsin, and plasmin itself. Potent activators have been demonstrated in plasma from patients with severe anoxemia[34] and amniotic fluid embolism,[3] and after electroshock, exercise, and administration of the pressor amines epinephrine, norepinephrine, and phenylephrine.[17] Small quantities of plasminogen activator exist in milk, saliva, tears, and seminal fluid.[51] Tissue activators of plasminogen, usually heat and acid stable, are located in the adrenals, uterus, lymph nodes, thyroid, and prostate. Very little, if any, exist in the heart, brain, or skeletal muscles.[2]

Urokinase, the urinary plasminogen activator, is of great clinical interest. A colorless proteolytic enzyme of extraordinary stability, urokinase may activate plasminogen by splitting arginine, lysine bonds, or both.

The activators of bacterial origin, streptokinase, staphylokinase, and other enzymes have long been under intensive investigation for

their possible use in the treatment of thromboembolic states.[51, 52] Technical complexities and allergic reactions have so far prevented the general application of fibrinolytic therapy in patients with vascular thrombosis.

Inhibition of Fibrinolysis

Evidence suggests the existence of two classes of substances that inhibit fibrinolysis: inhibitors of activation, and inhibitors of plasmin (antiplasmins). More knowledge is available concerning the plasmin inhibitors. The albumin fraction of plasma contains enough antiplasmin to inhibit plasma production through activation of all circulating plasminogen.[4] The normal alterations in fibrinolytic activity in man are probably more closely related to the quantity of circulating plasma activator than to a decrease in the normally-occurring inhibitors of activation.[27]

This distinction between the inhibitors of the formed product plasmin and the prevention of its formation is important clinically. Epsilon-aminocaproic acid (EACA),* originally described as a plasmin inhibitor, probably exerts its major antifibrinolytic action through inhibiting or restraining the activation of plasminogen.[5, 37]

Whether there is normally continuous intravascular coagulation and clot lysis is a disputed point. There is much evidence against it.[21, 37] Nevertheless, experiments on normal subjects at rest and under physiologic stress suggest that "normal fibrinolytic activity" reflects the presence of plasminogen activator in the circulation.[35, 45]

PATHOLOGIC STATES ASSOCIATED WITH FIBRINOLYSIS

Pathologic fibrinolysis occurs when the plasminogen activation exceeds normal inhibition. Excessive plasminogen activation results in hyperplasminemia, fibrin breakdown (fibrinolysis), multiple coagulation defects, and finally overt bleeding ("fibrinolytic purpura").

The conditions associated with hemorrhage from fibrinolysis are grouped into four main categories (Table 1).

STRESS. Enhanced fibrinolytic activity in relation to stress is well known.[37] Increased fibrinolytic activity occurs with surgical procedures,[30] exercise,[9] electroshock,[15] anoxia,[28, 56] prolonged tissue ischemia,[28] pyrogen administration,[26] and acute infection.[37] In view of the known association between electroshock and fibrinolysis, it is interesting that direct-current cardioversion appears to be without significant effect.[13]

As many as 45 per cent of patients with non-neoplastic disease undergoing surgical procedures demonstrated significant enhancement of fibrinolysis in one study.[42] The effect is transient, often parallels the degree of tissue trauma, and is most often present *without* abnormal bleeding. Occasionally, however, severe fibrinolysis with serious hemorrhage occurs with minimal operative trauma. Studies on patients under-

*Commercially available as Amicar (Lederle Laboratories).

Table 1. *Conditions Associated with Bleeding from Fibronolysis*

I. Stress[30, 58]

- A. Surgical procedures (particularly pulmonary[38, 42, 54] and cardiac[18, 39])
- B. Intensive exercise[9]
- C. Electroshock and burns[15]
- D. Anoxia[28, 56]
- E. Acute infection, pyrogen administration[26]

II. Obstetrical complications

- A. Abruptio placentae*[59]
- B. Amniotic fluid embolism*[3]
- C. Intrauterine retention of dead fetus[46]

III. Cancer

- A. Prostate[57]
- B. Gastrointestinal tract, female genital organs, bladder, pancreas[37, 44]
- C. Hemopoietic: polycythemia vera,[10] multiple myeloma,[53] leukemia[8, 12, 24, 41]

IV. Hepatic disease[19, 29, 43]

*Main cause of bleeding is liberation of thromboplastic substances with resultant intravascular clotting and eventual fibrinogen depletion.

going operations who bled excessively revealed three conditions: (1) hypofibrinogenemia without excessive fibrinolysis, (2) normal plasma fibrinogen with pathologic fibrinolysis, or (3) both hypofibrinogenemia and excessive fibrinolysis.

Recent interest has attended the discovery of pathologic fibrinolysis as a cause or contributing factor to the hemorrhage associated with pulmonary and open heart surgery.[38, 42, 58] During operations on the lung, plasminogen activator and thromboplastic material are released into the circulation, probably as a consequence of trauma.[54] In one study, 65 per cent of patients with hemorrhage during or after extracorporeal circulation demonstrated hypofibrinogenemia and increased fibrinolysis as determined by shortened euglobulin clot lysis time.[39] Another important observation is the finding that mixture of multiple individual plasmas through transfusion appears to increase fibrinolysis.[18] Epsilon-aminocaproic acid (EACA) is apparently capable of inhibiting this phenomenon. The exact mechanism of the pathologic fibrinolysis seen with extracorporeal circulation is not presently known.

Obviously, to what extent enhanced fibrinolytic activity in stress is physiologic and protective is unknown. Bleeding caused by stress fibrinolysis probably represents failure of the antifibrinolytic system to maintain normal restraint upon a process which is a natural adaptive phenomenon.

Drugs such as nicotinic acid may provoke fibrinolysis.[60] As many pressor amines are known to increase fibrinolytic activity,[17] it has been suggested that stress fibrinolysis may be mediated through catecholamines, although the exact mechanism is unknown. Incoagulability of the blood after sudden death, particularly from anoxia, has long been known.[33, 51]

Obstetrical Complications. Abruptio placentae,[59] amniotic fluid embolism,[3] and intrauterine retention of a dead fetus[46] *may* all be associated with fibrinolysis. Intravascular coagulation with eventual depletion of plasma fibrinogen ("defibrination syndrome") is probably responsible for most bleeding associated with amniotic fluid embolism. In some cases, however, increased fibrinolytic activity associated with a plasminogen activator in amniotic fluid has been observed.

With abruptio placentae, absorption of thromboplastic (clot-promoting) substances from retroplacental blood clots probably causes extensive intravascular coagulation and eventual defibrination.[50] Whether fibrinolysis is a common accompaniment and contributes additionally to the low plasma fibrinogen level is uncertain.[36] Patients with fibrinolysis often have low or absent plasma fibrinogen, because fibrinolysin, as noted before, has the ability to degrade fibrinogen as well as fibrin. This has understandably led to the confusion over the difference between bleeding caused by defibrination (liberation of thromboplastic substances leading to intravascular coagulation and subsequent hypofibrinogenemia) and that caused by primary clot digestion (fibrinolysis) with additional enzymatic degradation of plasma fibrinogen. Of course, hemorrhage in either circumstance will lead to further depletion of fibrinogen through extracorporeal loss. Actually, it is unlikely that these two processes operate separately without influencing the other.

Cancer. Fibrinolysis leading to hemorrhage may occur with almost any malignant disease,[37] but particularly with carcinoma of the prostate.[57] Cancers of the gastrointestinal tract, female genital organs, bladder, and pancreas[37, 44] have all been reported with fibrinolysis. An occasional patient with cancer, however, may demonstrate *decreased* activity.[49] Polycythemia vera,[10] multiple myeloma,[53] and leukemia[8, 12, 24, 41] are hematologic neoplasms in which fibrinolysis is often an unrecognized cause of bleeding. I recently observed hemorrhage secondary to fibrinolysis in a patient whose bone marrow demonstrated the proliferative phase of myelosclerosis (agnogenic myeloid metaplasia). Bleeding stopped with epsilon-aminocaproic acid (EACA) therapy. After treatment with radioactive phosphorus (^{32}P) and busulfan, fibrinolysin titers fell progressively and finally disappeared. Occurrence of fibrinolytic purpura in the course of hematologic malignant disease is often an extremely unfavorable prognostic sign.

Hepatic Disease. Augmented fibrinolytic activity with cirrhosis has been known for many years.[19, 29] Decrease in fibrinolytic inhibitors as well as pathologic activation of fibrinolysis has been demonstrated.[43] Exact determination of the cause of bleeding associated with hepatic disease is a complex clinical problem when thrombocytopenia, clotting factor deficiencies, and portal hypertension are also often present.

CHARACTER OF FIBRINOLYTIC BLEEDING

The character of bleeding from fibrinolysis varies, depending on the presence of significant hypofibrinogenemia and other clotting factor deficiencies. It is usually purpuric. Subcutaneous ecchymoses have an

unusual propensity for painful induration and ulceration, a feature which may possibly be related to irritation from proteolytic degradation products in the tissues. Large confluent ecchymoses are common. Petechiae are rare, and hemarthroses most unusual. Spontaneous, diffuse hemorrhage from the mucous membranes of the gastrointestinal and genitourinary tracts occurs, but probably less commonly than from thrombocytopenia. When significant depletion of plasma fibrinogen is present, or there are additional coagulation factor deficiencies, bleeding is more hemophilioid in character; hematuria, hemarthroses, retroperitoneal hemorrhage, and menorrhagia may all be seen. When fibrinolysis is associated with surgical trauma, diffuse oozing from the injured tissues of the operative bed is the rule. Careful attention should be paid to the development of large ecchymoses from needle injections. This may be the only sign of a potentially fatal fibrinolytic hemorrhagic diathesis.

PATHOLOGIC STATES ASSOCIATED WITH DECREASED FIBRINOLYTIC ACTIVITY

Decreased fibrinolysis has been noted in association with lipemia, congestive heart failure, and chronic renal disease.[37, 51] Evidence relating alterations in fibrinolytic activity to the pathogenesis of these conditions is inconclusive. The potential use of fibrinolytic substances in the treatment of thromboembolic disease, not considered here, has been thoroughly reviewed.[37, 51, 52]

DIAGNOSIS OF PATHOLOGIC FIBRINOLYSIS

The ideal fibrinolytic assay is not yet available. The simplest tests are often the slowest and least sensitive. By selectively choosing one or more of the procedures described, however, one can document fibrinolysis and follow the course of its treatment successfully in most patients.

WHOLE BLOOD CLOT LYSIS TIME. Normal whole blood will not lyse when incubated under sterile conditions. From 5 to 10 cc. of sterile blood is incubated at 37° C. In 15 and 30 minutes, if a clot has formed, the tube is left to be observed one and two hours, and finally, if the clot is still intact, overnight. *Dissolution of a formed clot is excellent presumptive evidence of fibrinolysis.* If the blood does *not* clot, fibrinolysin may be but is not necessarily present. Determination of plasma fibrinogen (normally 160 to 425 mg. per 100 ml.) is mandatory in patients with incoagulable whole blood. One cannot assume that low plasma fibrinogen is necessarily the result of fibrinolysis, although *hypofibrinogenemia is the most commonly recognized accompaniment of excessive fibrinolysis.* As already mentioned, hypofibrinogenemia may be the result of defibrination, and is also seen with serious hemorrhage from any cause, Waterhouse-Friderichsen syndrome, and transfusion of incompatible blood (probably an example of defibrination caused by the liberation of thromboplastin from hemolysed red blood cells).

If pathologic fibrinolytic activity is present, it may be impossible to

detect clotting of whole blood because fibrinolysis is too rapid to permit detection of a clot, the fibrinogen level is too low, the products of fibrin digestion are themselves anticoagulants, or various combinations of the first three. Although the whole blood clot lysis test, for the reasons stated, is relatively insensitive and slow, it has the advantage of utmost simplicity, low cost, and ready availability in an emergency.

Plasma Clot Lysis Time. In each of four tubes in a row 0.1 cc. of normal plasma is placed. To each tube 0.1 cc. of saline and 0.1 cc. of M/80 calcium chloride is added. When coagulation occurs, 0.1 cc. of the following is added to each: (1) undiluted test serum; (2) test serum diluted 1:2, 1:4, 1:8, and 1:16 (with normal saline); (3) physiologic saline; and (4) undiluted normal control serum. The preparation is incubated at 37° C. overnight and then observed for presence or absence of complete clot lysis.[22]

Euglobulin Lysis Time. This test is more sensitive and rapid than either the whole blood clot lysis time or the plasma clot lysis time. Lysis is less than two hours indicates pathologic fibrinolysis. In this test, fibrinolysis inhibitors are separated by water dilution and plasma acidification.[27] It is an excellent test for studying factors which influence activation. Since fibrinolytic inhibitors have been removed by the test, it is not ideal for following the course of patients receiving antifibrinolytic drugs.

Other Tests. Thromboelastography, synthetic substrates, fibrin plates, fibrin tagged with radioactive iodine, and immunologic techniques have all found special investigative applications in the study of the fibrinolytic system,[37, 51] but routine clinical application has not been achieved.

Every patient with spontaneous bleeding or excessive hemorrhage during or after operation should be studied for the possible presence of pathologic fibrinolysis. If fibrinolysis with hypofibrinogenemia is the sole cause of bleeding, theoretically the thromboplastin generation test should be normal. With severe fibrinolysis, however, the level of other coagulation factors is so often reduced and anticoagulants are so often present that first stage clotting assays (thromboplastin formation) are often abnormal and not helpful in a differential diagnosis.

TREATMENT OF FIBRINOLYSIS

Before the advent of an effective antifibrinolytic agent, treatment of bleeding was confined to an attempt at management of the underlying disease, together with replacement of blood, fibrinogen, and other clotting factors.

Epsilon-aminocaproic acid (EACA) is a monoamino carboxylic acid. It is believed to act through competitive inhibition of plasminogen activation. Plasmin (fibrinolysin) is also inhibited, but to a much lesser degree. EACA is well absorbed when given orally, and can be given intravenously. Maximum plasma concentrations are obtained in two hours after an oral dose. Urinary excretion is rapid with almost all the drug nonmetabolized.

Because of its high urinary concentration and its inhibition of the urinary plasminogen activator, urokinase, EACA has found special usefulness in the management of urinary bleeding from diverse causes, *even when evidence for pathologic systemic fibrinolysis is lacking.*[6] Bleeding in association with operations on the urinary tract (nephrectomy and prostatectomy), hemophilia, and thrombocytopenia has been reported to respond favorably to EACA therapy.[2, 37, 45] Indeed, urinary hemorrhage is probably the only situation in which the use of antifibrinolytic drugs is justified when evidence for systemic fibrinolysis is absent. Evidence has been presented for the value of EACA in controlling bleeding after prostatectomy for benign hyperplasia.[47] Naturally, the blood fibrinolytic activity should be tested routinely before operation in all patients suspected of having prostatic cancer,[57] even though fibrinolysis in this condition is usually restricted to patients with metastatic disease.

Antifibrinolytic therapy is not recommended for patients with casual or indolent hematuria (not requiring transfusion), because of the theoretic danger of inducing excessive coagulation with acute obstructive uropathy. In practice thus far, however, this danger has been more theoretic than real. I often initiate antifibrinolytic treatment in patients with urinary hemorrhage without fibrinolysis with half doses. The amount of drug should then be tapered rapidly as clots appear. Severe bleeding in association with metastatic prostatic carcinoma with fibrinolysis should be treated, however, with full doses of EACA.

Postpartum uterine hemorrhage has been reported to respond favorably to EACA.[1] The drug may interfere with endometrial activation of plasminogen. Antifibrinolytic therapy may be given in instances of abruptio placentae or retention *in utero* of a dead fetus, when fibrinolysis can be shown to be a major factor in bleeding. One must always remember that these two conditions, as well as amniotic fluid embolism, are often associated with diffuse intravascular coagulation. In this event, EACA is theoretically harmful because it increases the possibility of thrombosis. In the presence of the defibrination syndrome, the drug of choice may be heparin. Once this anticoagulant inhibits intravascular coagulation, activation of fibrinolysis ceases. Unusual clinical urgency and strong convictions are required, however, to justify initiation of heparin for bleeding. Even then, vigorous trial first of administration of fibrinogen and fresh whole blood is strongly favored. Since there is often great uncertainty whether fibrinolysis can definitely be incriminated as contributing to fibrinogenopenia in these obstetrical conditions, use of EACA is exceedingly dangerous. When reasonable doubt exists, I refrain from its use unless it appears that all other measures have been unsuccessful and the patient will die otherwise.

EACA has been reported to control bleeding in patients with hepatic cirrhosis and portal hypertension, undergoing vascular shunt operations.[20] One must always bear in mind the complex nature of bleeding associated with hepatic insufficiency. Unless pathologic fibrinolysis can be demonstrated, it seems unlikely that antifibrinolytic treatment will be beneficial.

Experience with EACA in the management of fibrinolytic purpura seen in leukemia, lymphoma, and the myeloproliferative disorders has been limited. The incidence of pathologic fibrinolysis in the hematologic malignant diseases is probably greater than realized. A trial of EACA is perhaps indicated in any patient with serious bleeding in whom fibrinolysis can be demonstrated and evidence for intravascular coagulation is lacking.

Antifibrinolytic therapy has proved useful in controlling hemorrhage associated with fibrinolysis during mediastinotomy and open heart surgical procedures, particularly for cyanotic congenital heart disease. While coagulation factor deficiencies do occur during or after extracorporeal perfusion, fibrinolysis is proving a more common cause of abnormal bleeding. It is wise for all candidates for open heart surgical procedures to have preoperative blood assays for pathologic fibrinolysis. I do not give EACA prophylactically to patients whose blood reveals no increase in activity. When the euglobulin lysis test is 45 minutes or less, however, the possibilities for troublesome bleeding due to fibrinolysis are so great that antifibrinolytic treatment is started preoperatively and maintained throughout the operation. When the result of the test is normal preoperatively, patients are observed carefully for the first sign of excessive loss of blood. The assay is then repeated, and, if the result is positive, treatment with EACA is begun.

Hemorrhage resulting from thrombocytopenia, unless into the urinary tract, is not controlled by EACA therapy, which also is not beneficial in bleeding from disrupted vessels or in states with increased capillary fragility.

Some minor adverse effects have been reported: diarrhea, dizziness, malaise, conjunctival suffusion, headache, nasal stuffiness, and rash.[5] The possibility of inducing thrombosis with antifibrinolytic drugs should always be kept in mind, even though the reported incidence has been exceedingly low.[5]

As teratogenic effects have been observed when EACA is administered during the first third of pregnancy in animal experiments, administration of the drug is not recommended during this period. No harmful effects have been recorded when given to animals during the first third of pregnancy.

Until the normal role of the fibrinolytic system in maintaining patency of the blood vessels is better understood, the low reported incidence of adverse reactions with EACA should not diminish the caution and judgment necessary before its administration in all circumstances. At present, use of EACA is justified in those situations in which serious bleeding is associated with fibrinolysis, and evidence for defibrination through intravascular thrombosis is absent. It may also be tried cautiously in patients with serious hemorrhage from the urinary tract, irrespective of the absence of demonstrable circulating fibrinolysin.

The initial dose of EACA is 5 gm., given either orally or by slow intravenous infusion. One gram may then be given every one or two hours if renal function is normal. From 12 to 15 mg. per 100 ml. is an

effective plasma level. More than 25 to 30 gm. in an adult in 24 hours is not recommended.

In fulminant hemorrhage due to fibrinolysis, I prescribe 5 gm. (20 cc.) of EACA diluted with physiologic saline solution as an infusion during the first 60 to 90 minutes of treatment. Maintenance therapy of 1 gm. hourly is given for approximately eight hours. The plasma clot lysis test is used to monitor the effects of treatment. Failure to inhibit or significantly decrease fibrinolysis and thereby control hemorrhage within this period is not often overcome by longer administration or use of larger doses. If available, serial thrombin time determinations are probably more sensitive, if not less convenient, than the plasma clot lysis test in following antifibrinolytic therapy.[11]

During hemorrhage, the concurrent administration of fresh whole blood is stressed. Only with plasma fibrinogen levels below 100 to 150 mg. per 100 ml. is fibrinogen infusion recommended. Even then, whole fresh blood alone may be adequate.

For less severe bleeding, oral therapy is satisfactory. After an initial 5 gm. dose, 2 to 3 gm. is given every three hours.

Other antifibrinolytic drugs are being intensively studied. Para-aminomethylcyclohexane carboxylic acid is 10 to 15 times more potent than EACA.[14] Additional agents are para-aminomethylbenzoic acid and the kallikrain inhibitor, Trasylol.[37] None of these agents, however, has been used as extensively as EACA.

CONCLUSIONS

Fibrinolysis is a cause of serious, often fatal, hemorrhage in a wide variety of clinical situations. The process is frequently undiagnosed. In patients whose bleeding is not due to trauma, spontaneous vascular disruption, thrombocytopenia, vitamin K deficiency, or other coagulation factor deficiencies, pathologic fibrinolysis is a likely cause or contributing factor. This is particularly true in patients who have been exposed to stressful situations such as extensive surgical procedures and those with malignant or hepatic disease. Laboratory confirmation of fibrinolysis of clinical significance is usually not difficult. If no evidence of intravascular clotting exists, judicious use of the antifibrinolytic agent, epsilon-aminocaproic acid (EACA), is often extremely effective in controlling bleeding.

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Unusual Cutaneous Manifestations of Drug Hypersensitivity

WILLIAM P. COLEMAN, M.D.*

Drug allergy is a common and important medical problem today. The steady growth in number and variety of available therapeutic products has resulted in an increasing incidence of adverse reactions to drugs. Although some of these reactions are definitely allergic, others are not. For example, urticaria from penicillin is allergic, but argyria is not. Toxic effects occur in direct relation to the amount of drug in the body, when an overdose of a drug is given. These effects frequently are exaggerations of the pharmacologic action of the drug. Absolute overdosage may result from inaccurately administered excessive dosage, or as in the case of iodides, from accumulation. The cumulative effect is also illustrated by the slate-blue discoloration of argyria in patients who have used silver-containing nose drops excessively, or by the yellowish color imparted to the skin when quinacrine is administered for long periods of time.[8, 9] Relative overdosage may take place in patients who, perhaps because of partial or complete renal failure, do not excrete drugs at an adequate rate. These effects are likely to occur in any patient if a threshold blood level is exceeded.

Hyperergic reactions are qualitatively similar to those induced by excessive dosage, but are produced by quantities harmless to most people. These effects are said to be due to increased individual susceptibility.[9]

True idiosyncrasy implies an inherent qualitatively abnormal reaction exemplified by jaundice from hemolytic anemia occurring in certain Negroes with congenital enzymatic defects when given primaquine as an antimalarial. Some of the erythrocytes of such reactors are deficient in specific enzyme, glucose-6-phosphate dehydrogenase.

Biotropic effect is a term used to describe activation of a latent cutaneous infection by a drug,[8] as exemplified by activation of herpes simplex lesions by barbiturates.

Reactions in the skin and elsewhere may follow the ecologic imbalance based on disturbances in the usually prevailing balance between the various species of microorganisms.[8] Overgrowth of Candida

From the Section on Allergy, Ochsner Clinic, New Orleans, Louisiana

albicans with resultant candidiasis of the anogenital areas after antibiotic therapy is an example. Glossitis which occurs after antibiotic therapy and black hairy tongue may also be explained by alteration of normal bacterial flora.

Allergic manifestations of drug therapy are not necessarily related to dosage, being produced frequently by a small amount of the drug. The chemical configuration of the drug, however, regularly influences allergic reactions, heterocyclic and unsaturated compounds being more prone. An induction period is required on initial exposure, but not on readministration. Allergic reactions occur in only a minority of persons receiving the drug and have no correlation with the known pharmacologic properties of the offending compound. They usually reappear on administration of the drug in small amounts. Frequently, symptoms are characteristic of allergic disorders in general, in that they may exhibit the prominent clinical features of anaphylaxis, urticaria, contact dermatitis, and asthma.[16] They may also be manifested by various rashes, polyarteritis nodosa, drug fever, serum sickness, and deleterious effects on blood, liver, or kidney.

Generally, allergic expressions result from reaction of antigen and antibody, and existence of various types of antibodies can be demonstrated in many patients with allergic disorders. In drug allergy, however, evidence of an allergic mechanism is rarely demonstrable, presumably because the drugs act as haptenes and not as complete antigens.[18] It is generally assumed that reactions are due to the presence of antibody against the drug itself, or against an antigenic conjugate between the drug and a protein of the blood or tissue.[20] This assumption is based in part on experimental studies by Landsteiner[12] and others, of the antigenicity of simple chemicals, and there is some evidence to support it in several types of reaction in human beings.[16] Furthermore, hypersensitivity reactions may be induced by degradation products of the administered drug in some instances. For example, penicillin allergy may be caused by penicillenic acid or penicilloic acid, which are degradation products of penicillin. The lack of adequate testing methods is a great obstacle to clinical investigation of drug hypersensitivity. In addition to the usual manifestations of allergy, a considerable variety of reactions which rarely, if ever, result from allergy to naturally encountered allergens may be caused by hypersensitivity to drugs. Such reactions include fever, many types of rashes, hepatitis, various hematologic effects, vasculitis, pulmonary infiltration, nephropathy, lymphadenopathy, and cardiopathy.[19] Table 1 lists some of the cutaneous manifestations of adverse reactions to drugs.

Certain drugs are apparently prone to produce cutaneous allergic reactions. Penicillin is the most common; other frequent offenders are the sulfonamides, mercurials, iodides, arsenicals, gold salts, streptomycin, barbiturates, quinine, thiouracils, hydantoin derivatives, bromides, and salicylates. Although space does not permit a complete listing of drugs that may produce eruptions, or of the types of eruptions produced by drugs, certain manifestations are well known and will be

helpful in making the diagnosis. For example, penicillin commonly produces urticaria, angioneurotic edema, or exanthemata, and may produce erythema multiforme. Bromides and iodides are known to produce acneiform and granulomatous lesions. Sulfonamides are associated with vesiculobullous, photosensitivity, pemphigoid, and psoriasiform eruptions. Table 2 itemizes some drugs that are prone to produce adverse cutaneous reactions. For compendia of other drugs reported to cause these conditions, the reader is referred to Alexander's excellent monograph of this subject.[2]

Almost all drugs are capable of producing erythematous and urticarial eruptions. Macular, erythematous eruptions are usually widespread, affecting the trunk, legs, and arms and at times being morbilliform or scarlatiniform. Table 3 contains some cutaneous manifestations of drug allergy and some of the drugs which can incite these reactions.

The three most common dermatologic expressions of drug allergy are contact dermatitis, urticaria, and exanthemata.[2] In this discussion

Table 1. *Adverse Cutaneous Reactions to Drugs*

Acneiform	Morbilliform
Angioneurotic edema	Nail changes (onycholysis, etc.)
Allergic vasculitis	Photosensitivity reactions
Bullous eruptions	Pigmentary changes
Circumscribed bromodermas and iododermas	Proctitis
Contact dermatitis	Pruritus
Eczematous	Purpura
Erythematous	Scarlatiniform
Erythroderma	Stevens-Johnson disease
Erythema multiforme-like eruption	Stomatitis
Erythema nodosum-like eruption	Toxic epidermal necrolysis
Exfoliative erythroderma	Tumors and tumor-like reactions
Fixed eruption	Ulcerating
Furunculoid	Urticaria, including serum sickness-like and anaphylactoid reactions
Gingivitis	Vegetating
Glossitis	Vesicular
Lichenoid and lichen planus-like	

Table 2. *Some Drugs Which Frequently Cause Adverse Cutaneous Reactions*

Allyl-isopropyl-acetyl-carbamide (Sedormid)	Penicillin
Acetanilid	Phenolphthalein
Acetophenetidin	Phenylbutazone
Aminopyrine	Phenothiazine
Antipyrine	Pollen extracts
Arsenicals	Quinacrine
Barbiturates	Quinine
Bromides	Quinidine
Chloramphenicol	Salicylates
Cinchophen	Serums
Diphenylhydantoin	Streptomycin
Gold salts	Sulfobromophthalein
Iodides	Sulfonamides
Mercurials	Thiouracil

Table 3. *Selected Cutaneous Manifestations of Drug Allergy and Some Drugs That May Cause Them*

REACTION	DRUG
Erythema multiforme-like	Acetophenetidin, aminopyrine, antihistamines, antipyrine, arsenicals, barbiturates, bromides, chloramphenicol, cinchophen, diphenylhydantoin, gold salts, phenolphthalein, phenylbutazone, salicylates, streptomycin, sulfonamides, bismuth, phenothiazines, chlorpropamide, penicillin, and iodides.
Stevens-Johnson disease	Antipyrine, belladonna, salicylic acid, quinine, mercurials, arsenicals, phenylbutazone, phenobarbital, and sulfonamides.
Erythema nodosum-like	Iodides, bromides, sulfonamides, penicillin, and salicylates.
Bullous drug eruptions	Arsenicals, bromides, iodides, mercurials, sulfonamides, quinine, antipyrine, phenolphthalein, barbiturates, salicylates, chloral hydrate, diphenylhydantoin, penicillin, aloin, acetophenetidin, aconite, aminopyrine, antipyrine, atropine, bismuth, cinchophen, digitalis, ergot, gold salts, and streptomycin.
Toxic epidermal necrolysis	Isoniazid, penicillin, phenolphthalein, antipyrine, barbiturates, hydantoin-type anticonvulsants, sulfones, sulfonamides, and phenylbutazone.
Purpura	Carbamides (Sedormid), iodides, sulfonamides, arsenobenzols, bismuth, arsenicals, quinine, quinidine, gold salts, barbiturates, nirvanol, salicylates, insulin, digitoxin, acetophenetidin, antihistamines, antipyrine, ergot, griseofulvin, phenylbutazone, thiouracils, bromides, cinchophen, and diphenylhydantoin.
Allergic vasculitis	Penicillin, sulfonamides, thiouracils, chloramphenicol, chlortetracycline, phenylbutazone, busulfan, pyromen, iproniazid, and iodides.
Exfoliative dermatitis	Arsenicals, barbiturates, gold salts, mercurials, quinacrine, phenylbutazone, penicillin, sulfonamides, phenothiazines, chlorpropamide, diphenylhydantoin, bismuth, iodides, streptomycin, and aminosalicylic acid.
Fixed drug eruptions	Phenolphthalein, barbiturates, antipyrine, acetophenetidin, aminopyrine, phenylbutazone, penicillin, arsenicals, antimony, iodides, mercurials, quinine, gold salts, salicylates, and sulfonamides.
Lichenoid and lichen planus-like reactions	Arsenicals, chloroquine, quinacrine, gold salts, quinidine, para-aminosalicylic acid, thiazides, and propylthiouracil.
Acneiform eruptions	Bromides, iodides, corticotropin, corticosteroids, cyanocobalamine, and certain contactants.
Bromodermas and iododermas	Bromides and iodides.
Tumors and tumor-like	Arsenicals, iodides, bromides, and diphenylhydantoin.
Serum sickness-like	Penicillin, streptomycin, sulfonamides, thiouracils, barbiturates, bismuth, digitalis, diphenylhydantoin, insulin,

Table 3. *Selected Cutaneous Manifestations of Drug Allergy and Some Drugs That May Cause Them* (Continued)

REACTION	DRUG
	iodides, salicylates, quinidine, phenylbutazone, mercurials, and arsenicals.
Photosensitive	Sulfonamides, sulfonylurea hypoglycemic agents, chlorothiazides, phenothiazine, demethylchlortetracycline, griseofulvin, quinine, gold salts, and psoralens.
Contact-type	Arsenicals, local anesthetics, mercurials, penicillin, quinacrine, streptomycin, sulfonamides, antihistamines, gold salts, iodides, neomycin, menthol, ephedrine, and salicylates.

of some of the more unusual cutaneous manifestations of drug allergy, what is meant by unusual is eruptions that are infrequently encountered in the average general medical practice. All reactions discussed are not extremely unusual in a busy dermatologic practice. Drug eruptions may not be recognized if they are not suspected, since they can mimic many cutaneous diseases. Many of the exceptional reactions to be discussed are alarming, but they are not common, and most of them are by no means disastrous. Awareness that they can occur makes it easier to recognize them and deal with them promptly.

Erythema Multiforme

As the name implies, erythema multiforme consists of a number of different lesions (macules, papules, vesicles, and others) which vary greatly in size and configuration. It may be classified as idiopathic or symptomatic. The former is characterized by recurrent attacks at regular intervals, usually in the spring or autumn. The eruption is acute, polymorphous, exudative, bright or dark red, and symmetrically distributed. The lesions may be macular, papular, urticarial, bullous, or hemorrhagic. Target lesions (erythema iris) may occur. The main sites of predilection are the upper part of the face, the neck, forearms, legs, and dorsal surfaces of the hands and feet. The symptomatic types of erythema multiforme include polymorphous, erythematous, vesicular, and bullous toxic eruptions that develop in association with serum sickness and allergic purpura and with systemic or visceral diseases such as infectious mononucleosis, brucellosis, rheumatic fever, typhoid fever, pneumonia, diphtheria, endocarditis, pericarditis, nephritis, or with drug eruptions.[3] Iodides, sulfonamides, antipyrine, hydantoins, phenobarbital, bromides, gold salts, and penicillin, among others, have been implicated. The eruption is characterized by the bright color, tendency to be symmetrical, predilection for the dorsal surfaces of the distal extremities, tendency to form ringed lesions, and absence of itching. Figure 1 illustrates iris lesions of erythema multiforme, which occurred after administration of antipyrine.

Figure 1. Erythema iris with depigmentation.

Stevens-Johnson Disease

Stevens-Johnson disease, also known as ectodermosis erosiva pluriorificialis, is severe and often fatal. It may be classified as a type of erythema multiforme (erythema multiforme exudativum or erythema bullosum malignans) or as a distinct entity.[3] The onset is abrupt, with fever to 104° F., headache, malaise, and soreness of the throat and mouth. Constitutional symptoms follow including rapid, weak pulse, tachypnea, prostration, and arthralgia. Vesicular lesions develop on the lips, tongue, and buccal mucosa. These progress, forming pseudomembranes with bleeding and ulceration. Other mucous membranes become involved including conjunctival, nasal, urethral, vaginal, and anal. Vesiculobullous or petechial and hemorrhagic eruptions may involve the face, hands, and feet especially. Erosive balanitis and vaginitis may be severe. Bronchial pneumonia may develop.

Stevens-Johnson disease may be idiopathic or associated with pregnancy, food allergy, deep roentgen-ray therapy, or malignant disease.[3] It may occur as a manifestation of drug hypersensitivity. The idiopathic form typically affects children and young men, most often in winter and spring. It may begin with herpes simplex lesions in or around the mouth, and the virus of herpes simplex may be important in the pathogenesis of this form of the disorder. The disease may cause panophthalmitis and blindness. It is sometimes fatal. There are no specific laboratory findings.

Figure 2. Stevens-Johnson disease.

Some drugs which may cause Stevens-Johnson disease include antipyrine, belladonna, salicylic acid, quinine, mercury, arsenic, phenylbutazone, phenobarbital and the sulfonamides. Treatment includes withdrawal of the offending drug, supportive measures, and administration of corticosteroids. Antibiotics are ineffective. Figure 2 shows a patient with Stevens-Johnson disease due to phenobarbital. Fatal Stevens-Johnson disease developed in another young woman, who had been hospitalized for eclampsia, when inadvertently given phenobarbital for sedation. She suffered complete exfoliation of the skin.

Erythema Nodosum

Erythema nodosum is often classified as a type of erythema multiforme, to which it is closely related. The eruption consists of bilateral, symmetrical, nodular, tender lesions on the shins. The nodules vary from 1 to 5 cm. in diameter. The skin over the nodules is smooth and shiny, ranging from red to bluish-brown. Ulceration and exudation occur rarely, if ever, and the mucosa is not affected. The lesions appear in successive crops, and after a few days or weeks, undergo slow involution. The onset is associated with usually mild constitutional symptoms including fever, malaise, and pain in the muscles and joints. The lesions, usually ranging from two to six, are symmetrical, and commonly occur on the shins but may be found on other parts of the limbs, the buttocks, or the face. Dermatitis contusiformis is a synonym for this disorder. As the name implies, the lesions may resemble contusions.

The idiopathic form occurs chiefly in young women during the spring and autumn. Attacks are frequently recurrent and may continue to recur for years, being seasonal in some instances. Vascular hypersensitivity to bacterial products, especially streptococcal and tubercle bacilli, may cause this disorder. Other conditions frequently associated with erythema nodosum are rheumatic fever, leprosy, coccidioidomycosis, endocarditis, pericarditis, certain other infectious diseases, and sarcoidosis.[3] Ingestion of certain drugs, especially iodides, bromides, sulfonamides, and salicylates, may cause erythema nodosum. Treatment consists of withdrawal of the offending drugs, rest, and supportive measures; administration of corticosteroids is sometimes beneficial.

Vesiculobullous Drug Eruptions

Vesiculobullous drug eruptions may be considered a distinct entity or a form of erythema multiforme (erythema multiforme bullosum). Barbiturates, arsenicals, bromides, and iodides are the commonest drugs causing this type of eruption, which may become hemorrhagic and even fatal. Included among the many drugs which may cause vesiculobullous eruptions are sulfonamides, quinine, antipyrine, phenolphthalein, salicylates, chloral hydrate, phenobarbital, diphenylhydantoin, and penicillin. Psoralens, used for treatment of vitiligo or as an aid to sun-tanning, may produce vesiculobullous eruptions upon exposure to sunlight. I recently saw a patient with hemorrhagic bullous eruptions as a manifestation of a fixed drug eruption from barbiturates. Fixed drug eruptions and photosensitivity reactions will be discussed more fully later.

Although epidermolysis bullosa is generally considered an inherited process, starting in early life and characterized by bullous formation and erosions of the skin secondary to minor trauma, it occasionally occurs in adulthood. The acquired form has apparently sometimes followed severe drug reactions, notably from sulfonamides and arsenicals.[5]

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis is a special cutaneous bullous drug eruption that is so severe that it has the appearance of an extensive scalding burn. Erythema occurs at first in patches, which progress to generalized erythema, in most cases with branny scaling, and bullae with extensive denudation of the skin. It is the complete denudation of the skin over the entire body which is characteristic of this form of drug reaction.[3, 8] Within a few hours the condition becomes extremely grave, and may prove fatal in a few days, usually from sepsis or from electrolyte imbalance as a consequence of fluid loss. Drugs implicated have been isoniazid, penicillin, phenolphthalein, antipyrine, barbiturates, hydantoin-type anticonvulsants, sulfones, sulfonamides, and phenylbutazone.

Purpura

Purpura due to drugs is uncommon, but it has been reported in connection with a large number of different substances, particularly

Sedormid (allyl-isopropyl-acetyl-carbamide), the arsenobenzol compounds, combined bismuth and arsenic therapy, and sulfonamides.[1] Some other drugs that can produce purpura are bismuth, quinine, quinidine, gold salts, iodides, barbiturates, aleurate (allyl-isopropyl-barbituric acid), nirvanol, salicylates, insulin, tetra-ethyl-ammonium chloride, digitoxin, ergot, griseofulvin, phenylbutazone, thiouracils, antipyrine, bromides, cinchophen, and diphenylhydantoin. Purpura has also been reported to develop from inhalation of menthol and exposure to DDT insecticide.[1] It may be the sole expression of drug hypersensitivity. It may be nonthrombocytopenic or be associated with thrombocytopenia. A few drugs, such as phenylbutazone, produce both types.

Characteristic lesions include petechiae, ecchymoses, hematomas, or spontaneous genitourinary or gastrointestinal bleeding. The hemorrhagic lesions may affect skin or mucous membranes. The cutaneous lesions are widely variable and tend to recur. Purpura may occur alone or in association with erythema, effusions, or necrosis of the skin, or as a manifestation of erythema multiforme. Although the mechanism of development of purpura is not clear, increased capillary permeability and fragility are present.[13] When articular involvement and gastrointestinal bleeding occur with purpura, the condition is known as Henoch-Schoenlein purpura. Nephritis may accompany purpura and may be a serious or fatal complication. Purpura may be associated with infections, particularly with streptococcal organisms. It has also been associated with food allergy, vitamin C deficiency, certain snake bites, and disorders characterized by the presence of abnormal serum proteins.[13]

Allergic Vasculitis

Allergic vasculitis is characterized by manifestations in several body systems, most often the skin, musculoskeletal system, lungs, kidneys, and peripheral nerves. It may be initiated by an allergic reaction to a drug, or it may develop after an infection; sometimes no initiating factor is present. The allergic nature is inferred by such factors as history of allergy, hyperglobulinemia, eosinophilia, and the like. The diagnosis is made by biopsy. It appears that antigen and antibody unite to form large molecular complexes which somehow become attached to endothelial cells in small blood vessels where local inflammatory reactions are induced, presumably because of release of irritating substances from affected cells.[14] Some cases accompany rheumatoid arthritis and chronic leukemia, which are commonly associated with immunologic disturbances.[14] Although systemic vasculitis may be an autoimmune disorder, in some instances, it is known to occur as a manifestation of drug allergy. Cutaneous manifestations of allergic vasculitis include purpura, erythematous rash, inflammatory nodules, and urticaria. The drugs most frequently implicated in severe vasculitis are penicillin, sulfonamides, thiouracil, chloramphenicol, chlortetracycline, phenylbutazone, busulfan, pyromen, iproniazid, and iodides.[14]

Exfoliative Dermatitis

Exfoliative dermatitis is, as the name implies, a condition in which

the superficial skin is shed. It is characterized by universal or extensive obstinate scaling, itching erythroderma, and is usually associated with alopecia. Secondary infection is frequent. The lesion may follow a variety of dermatoses such as psoriasis, seborrheic dermatitis, and lymphoblastomas of the skin as well as eczematoid and scarlatiniform expressions of drug hypersensitivity.[3] When due to drugs, it is serious and may be fatal. It may last weeks or months even after withdrawal of a drug that has been recognized as its cause. Arsenicals, barbiturates, gold salts, mercurials, quinacrine, phenylbutazone, penicillin, sulfonamides, phenothiazines, chlorpropamide, diphenylhydantoin, and aminosalicylic acid are some of the drugs known to have caused exfoliative dermatitis.[3, 8] Withdrawal of the offending agent and corticosteroid treatment may be lifesaving in severe cases.

Fixed Drug Eruptions

Adverse reactions to drugs can mimic virtually any cutaneous disease, and therefore, in most suspected drug eruptions, other cutaneous diseases must be considered in the differential diagnosis. Fixed eruptions, however, are an exception, because they are almost pathognomonic of drug sensitivity.[4] The term is used to denote those cutaneous lesions that, once they have appeared at a given site after exposure to a drug, usually by ingestion, will reappear at approximately the same sites on subsequent administration.

The eruption has been reported after the ingestion of certain foods, such as tomatoes,[6] and even after physical and psychic stress. The most characteristic form is sharply circumscribed, round or oval areas of varying size. Edema develops first, followed by erythema, which darkens. The lesions may be eczematous, urticarial, vesicular, bullous, nodular, follicular, or herpetiform. At times ulcerations may appear. Residual pigmentation is common. Mucous membranes may be involved. With repetitions additional lesions may appear. A classic example of this is erythema perstans with pigmentation caused by phenolphthalein, the active ingredient in many laxatives.[3] Besides phenolphthalein, other drugs that may be associated with fixed drug eruptions include barbiturates, antipyrine, acetophenetidin (phenacetin), aminopyrine, phenylbutazone, penicillin, arsenicals, antimony, iodides, mercurials, quinine, gold salts, salicylates, and sulfonamides. The lesions usually react violently to even small test doses of the offending agent, and therefore serious consequences may result from giving even minute amounts of the drug for testing purposes.[4]

Fixed drug eruptions have been studied by means of skin graft exchanges with normal subjects. The attempt to demonstrate that the "shock site" is in the epidermis or cutis, as had been previously reported, was unsuccessful.[22] It was concluded that regional hypersensitiveness in these instances involves the deeper structures, probably the blood vessels.

Lichenoid and Lichen Planus-Like Eruptions

Lichenoid eruptions and lesions that resemble lichen planus may be manifestations of drug hypersensitivity. Some drugs that may induce

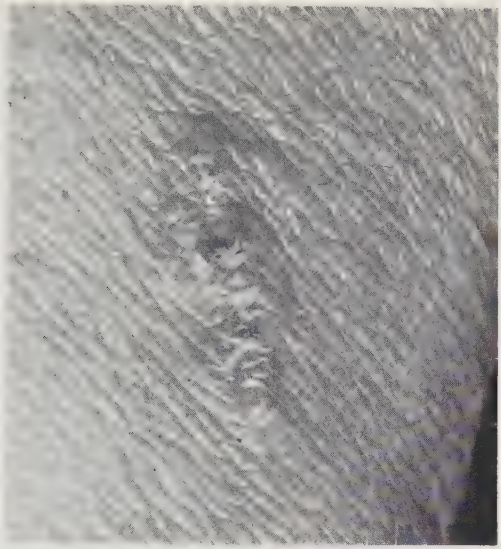

Figure 3. Lichen planus-like eruption caused by atabrine, illustrating the Koebner phenomenon.

this type of reaction are arsenicals, chloroquine, quinacrine, gold salts, quinidine, para-aminosalicylic acid, thiazides, and propylthiouracil. Figure 3 shows a patient with a lichen planus-like drug eruption produced by atabrine. An atypical lichenoid dermatosis due to prolonged administration of quinacrine has been described.[15] The plaques involved skin and mucous membranes. Although the lesions resembled fixed eruptions, they were histologically identical with lichen planus.

Acneiform Eruptions

Acneiform eruptions are characteristic of sensitivity to bromides and iodides. The term is derived from the fact that they resemble acne. Although bromides and iodides are not as freely employed in pure form for medicinal purposes as they were formerly, they are still administered in occult forms.[4] Iodized salt may be a source of exposure. Bromide is found in pentamethonium and other drugs, for example, the bromide salts in banthine and scopolamine. Iodides are also in some therapeutic vitamin preparations containing minerals and in certain food substitutes for weight reduction, such as Metrecal.[4] Allergic shocklike reactions, acneiform eruptions, and furunculosis have been known to follow intravenous administration of various iodide preparations used as contrast media for radiographic examinations. Other drugs which may produce acneiform eruptions include corticotropin, corticosteroids, cyanocobalamine (vitamin B_{12}), testosterone, progesterone, and contraceptive compounds; contact with petroleum products, lubricating oils, tar, and chlorine may also cause such eruptions.[3]

Circumscribed Bromodermas or Iododermas

Circumscribed bromodermas or iododermas may arise after administration of bromides or iodides. They may resemble pyodermas.

Figure 4. Bromoderma mimicking discoid lupus erythematosus.

Depigmentation of the affected areas may occur upon withdrawal of the offending drug, but in contrast to the depigmentation seen in lupus erythematosus, pigmentation tends to return. The lesions may resemble granulomas or erythema multiforme. Pseudoepitheliomatous hyperplasia may develop to such an extent that the clinical features and pathologic picture may resemble epitheliomas.[3] Figure 4 shows a patient with a bromoderma on the scalp.

Tumors and Tumor-Like Reactions

Tumors and tumor-like reactions, both benign and malignant, may be produced by drugs. For example, prolonged administration of arsenic in Fowler's solution and in other medications years later may produce superficial basal cell epitheliomas, usually on the trunk, or warty lesions (arsenical keratoses) on the palms and soles which may become squamous cell carcinomas. Although the characteristic iodide or bromide eruption is a follicular acneiform or furunculoid lesion, benign tumors may also develop. Diphenylhydantoin may cause generalized lymphadenopathy, and has been reported to produce a syndrome indistinguishable from malignant lymphoma.[17] Figure 5 shows arsenical keratoses and Figure 6 illustrates an epithelioma in a patient with arsenical keratoses.

Serum Sickness-Like Reactions

One of the most characteristic allergic reactions from drugs is a syndrome which has all the clinical features of serum sickness. After an incubation period of one or two weeks after administration of a drug, fever, urticaria, often with angioneurotic edema, arthralgia, and lymphadenopathy may develop. At times peripheral neuritis, other central

nervous system manifestations, erythemas, generalized periarteritis, other eruptions, and renal, cardiovascular, and gastrointestinal manifestations may occur. These symptoms may last two or three weeks or longer and gradually subside. In rare instances they may last as long as one year.[8] Although the clinical picture is identical to that of serum sickness, the immunologic features of true serum sickness are absent.

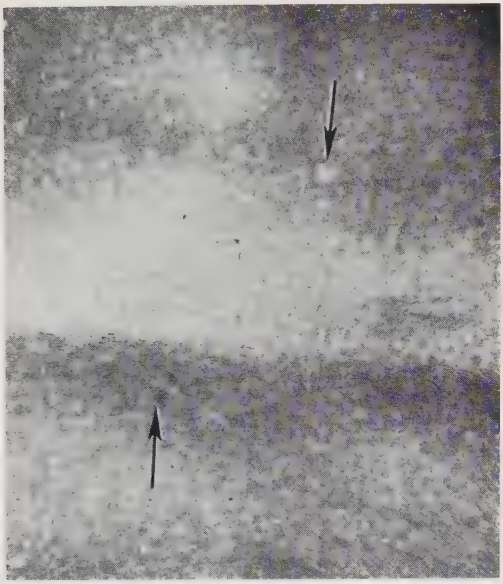

Figure 5. Arsenical keratosis, with hyperpigmentation and hypopigmentation. The appearance has been described as resembling raindrops on a dusty road.

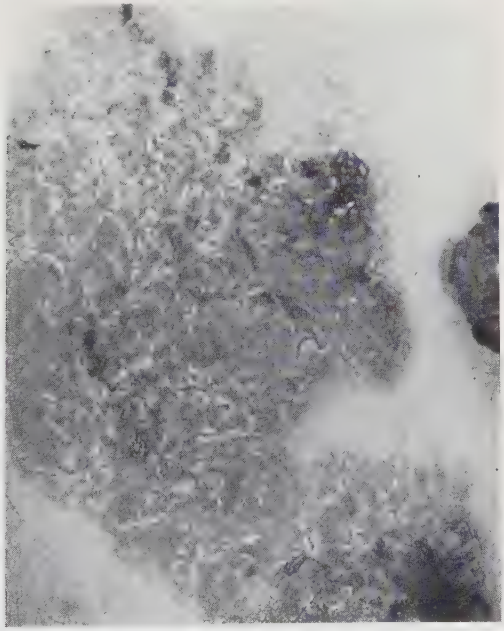

Figure 6. Epithelioma developing in a patient with arsenical keratosis.

Results of skin tests with the offending drugs are usually negative during and after the reaction, and antibodies are rarely demonstrable.[19] Penicillin is the most common offender. Streptomycin, sulfonamides, thiouracil, arsenicals, barbiturates, bismuth, digitalis, diphenylhydantoin, insulin, iodides, salicylates, quinidine, phenylbutazone, and others may also be associated with the serum sickness-like reaction

Photosensitivity Reactions

Physical allergy is concerned with hypersensitivity to heat, cold, light, or mechanical irritation, contact with which produces one of the allergic disorders. Hypersensitivity to light is the most important of these, and the most common of the dermatoses caused by physical agents. Light is the etiologic agent in polymorphic light eruptions, solar urticaria, contact photodermatitis, and endogenous photochemical dermatitis. Light is a major precipitating factor in certain cutaneous diseases associated with porphyria, psoriasis, pityriasis rubra pilaris, keratosis follicularis, pellagra, lupus erythematosus, acne rosacea, herpes simplex, xeroderma pigmentosum, actinic keratosis, cancer and keratoacanthoma.[10] Thus, it may be induced through mechanisms involving metabolic diseases, vitamin deficiency states, systemic disease, idiopathic disorders, or exposure to a photosensitizing agent.

Photosensitivity reactions are usually divided into two categories: phototoxic and photo-allergic. In the *phototoxic reaction* tissue damage is produced by chemical changes which occur as a result of light absorption by the drug and transfer of the absorbed energy to adjoining molecules. This effect leads to oxidative reactions and damage to tissue. This process requires a photosensitizing agent, and adequate light at the proper wavelength. It will occur in almost everyone so exposed. It resembles an intensified sunburn. In the *photo-allergic reaction*, radiant energy absorbed by the drug alters the drug itself or causes conjugates with tissue protein and formation of complete antigen. Presumably, the patient's allergic response to this complete antigen results in the reaction.[11] In contradistinction to phototoxic reactions, photo-allergic reactions occur in only a small percentage of persons exposed to the drug and the proper light, require an incubation period for sensitization, and often resemble other forms of cutaneous reactions known to be associated with allergy; in many cases a positive photopatch test can be elicited which has the characteristics of an allergic reaction.[11] Although in general the exposed areas of the skin are involved, the eruption may occur under lightly covered areas, and in the case of photo-allergic drug reactions, flare-ups may occur at unexposed sites distant from the exposed sites. The phenomenon of photo cross-sensitization to immunochemically related allergens may be demonstrated.[11]

In the photo-allergic reaction, the eruption may be papulovesicular, bullous, urticarial, eczematous, or exudative. Photosensitivity may occur from contact of the skin with coal tar, creosote, asphalt, fluorescin, eosin, oil of bergamot, citron oil, lime, figs, parsnips, buckwheat, okra, and sulfonamides.[3] Some of the drugs taken internally that are associated with photosensitivity reactions are sulfonamides, sulfonylurea hypoglycemic agents, such as tolbutamide and chlorpropamide, chlorothia-

zide, phenothiazine, demethylchlortetracycline, griseofulvin, quinine, gold, and psoralens. Onycholysis, seen in patients taking demethylchlortetracycline, is an example of a phototoxic type of photosensitivity reaction.[8] Bithionol and salicylanalides, bacteriostatic agents used in many proprietary topical preparations such as soaps, shampoos, antiseptic creams, and acne preparations, have been shown to act as photosensitizers, producing contact photodermatitis.[10]

Management of photosensitivity reactions includes avoidance of sunlight, and topical application of sunscreening agents as well as withdrawal of photosensitizing drugs. Also, if the eruptions are severe and extensive, systemic administration of corticosteroids may be indicated. Topical treatment with corticosteroid-containing preparations and oral antimalarial drugs is often helpful.

Contact Dermatitis

Since contact dermatitis from drugs is the most common manifestation of drug hypersensitivity, it will not be discussed in detail. Certain aspects, however, are pertinent to this discussion. Although contact dermatitis is used to describe a form of eczematous eruption due to an external contactant to which the patient is sensitized, identical eruptions can sometimes be produced by the same contactant through the blood if administered internally. Eczematous dermatitis may be caused by many agents other than drugs, such as bacteria, parasites, foods, chemical irritants, and seborrhea. Although usually general, the sensitized area of the skin may be strictly localized. Drugs may be suspected if there is a history of their use, especially those known to be allergenic.

Itching, erythema, and vesiculation are prominent features of the onset of allergic eczematous contact dermatitis. Pustulation and necrosis are complications, and dry, thickened, itching skin typifies the chronic form. This is true both of the contact type from allergens applied to the skin, and of the disseminated form from ingestion of drugs. Although the former is by far the more frequent, the two are intimately related. For instance, established contact dermatitis from a sulfonamide compound applied to the skin may be exacerbated by ingestion of the drug, or the eruption may be induced primarily by internal administration. The essential lesion is apparently the same in both (a fact not entirely agreed upon), namely edema with vesiculation within the epidermis. The causative substance is identified from the history and patch test. The patient's occupation is important; for example, contact dermatitis on the fingers from penicillin or streptomycin is encountered most often in pharmacists, nurses, physicians, or others who prepare these solutions. Dentists are prone to get contact dermatitis on the hands from local anesthetics. Localization of the dermatitis is of great importance in determining the offending contactant. The reader is referred to Walbott's excellent monograph on this subject[21] for details. Some drugs that induce contact dermatitis are arsenicals, local anesthetics, mercurials, penicillin, quinacrine, streptomycin, sulfonamides, antihistamines, gold salts, iodides, neomycin, menthol, ephedrine, and salicylates.

Both the contact type of cutaneous reaction and the immediate

reaction of urticaria or the serum sickness syndrome can occur simultaneously. For example, subjects with reactions to orally administered or intramuscularly injected penicillin may have, in addition to evidence of serum sickness (fever, urticaria, angioneurotic edema, arthralgias, morbilliform rash), patchy areas of blistering dermatitis resembling that produced by contact. The latter areas signify concomitant delayed contact type skin sensitivity if patch test with penicillin produces positive responses.[7]

SUMMARY

Adverse reactions to drugs present a growing problem to the physician. The increasing incidence of these adverse reactions parallels the expanding use of pharmaceutical agents in treatment of disease. Adverse reactions may be toxic, cumulative, hyperergic, or allergic, or due to true idiosyncrasy, biotropic effect, ecologic imbalance, or emotions. The only satisfactory treatment of a drug reaction is to discontinue use of the causative drug. Corticosteroid treatment may be indicated if the reaction is severe enough to be life-threatening.

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Late Manifestations of Breast Cancer

ALBERT SEGALOFF, M.D.

In general, the manifestations of malignant disease including those originating in the mammary gland can be divided into two categories. The first is due to the space-occupying aspect of the physical presence of the tumor and the second to products produced by the tumor which have a physiologic effect at a distant site, and may well be termed "humors from tumors."

MANIFESTATIONS DUE TO METASTASIS

The most common site for postoperative recurrence of breast cancer is in the region where the mastectomy was done together with the lymph nodes draining the area which were not removed, such as supraclavicular nodes and internal mammary nodes. The next most common site is the skeleton, with special predilection for the flat bones and the lumbar spine, metastases rarely being seen in the phalanges and associated parts of the hand and foot. Solitary metastasis to the mandible is equally unusual.

Surprisingly, metastases to the ovaries and pituitary gland are common and, indeed, may destroy the function of these organs and produce a seemingly spontaneous remission, in reality equivalent to surgical extirpation of the organs. Complete destruction with its physiologic consequences however, is indeed rare. Visceral metastases, particularly to the liver, lungs, and associated structures, and to the central nervous system, occur often but rarely as the sole site of initial metastases.

A major site of metastasis of breast cancer is bone. Unfortunately, osseous metastasis often occurs and progresses without producing pain or radiographic changes which would lead one to suspect its presence. Apparently, the metastasis is primarily in the marrow cavity with secondary erosion of bone. This would explain the anemia without roentgenography or other physical abnormalities. On marrow aspiration one finds that the malignant disease has replaced enough bone marrow to induce the anemia. This does not necessarily mean a poor prognosis, and these patients tend to respond to conventional therapy for the

From the Section on Endocrine Research, Alton Ochsner Medical Foundation, New Orleans, Louisiana

metastatic malignant lesion as well as any other patients with osseous metastases.

Manifestations due to the space-occupying feature of the tumor are unusual if the tumor is in one of the less common sites or is considerably smaller than the secondary lesion so that the physician does not suspect that the symptoms are due to breast cancer.

One of the rare manifestations of breast cancer is diabetes insipidus due to metastasis in the hypothalamohypophyseal tract. This can be managed by the usual means of controlling diabetes insipidus.

Some manifestations of breast cancer are unusual because metastasis may not occur until years after mastectomy. We have seen women who complained of severe back pain or, somewhat more commonly, a pathologic fracture, ten or more years after mastectomy. Therefore, the physician must be alert to the fact that neurologic, osseous, or visceral manifestations of distant metastases may occur in women even though five years has elapsed since mastectomy and they are supposedly cured.

Fortunately, carcinoma en cuirasse, infiltrating the entire anterior skin of the chest wall and frequently breaking it down, is rare. This condition is exceedingly difficult to manage as it gets infected and odorous. The known difficulties of managing such patients make one shy away from them, but it should be remembered that antibiotics, enzyme-containing ointments, and assiduous local care make this manifestations easier for the patient to live with.

MANIFESTATIONS DUE TO HUMORAL AGENTS

Carcinoma of the breast produces materials probably similar to those produced by other tumors. Increases in the thyroxine-binding globulin transcortin have been noted in some patients, but this is the exception.

The commonest humor from breast cancer is a substance or substances which produce hypercalcemia and osteopenia. This has recently been shown, with a high degree of probability, to be closely related to 7-dehydrocholesterol and therefore a sterol related to provitamin D rather than proteinaceous in nature like parathyroid hormone.[1] The hypercalcemia differs from that of hyperparathyroidism in two major particulars. Hypercalcemia of hyperparathyroidism is usually associated with either a normal or low phosphorus level in the serum. The unusual case with high serum phosphorus is generally associated with renal failure. Hypercalcemia of breast cancer, on the other hand, is most commonly associated with hyperphosphatemia. The two major types of hypercalcemia differ also in that the hypercalcemia of breast cancer usually disappears after administration of an adequate amount of corticoid, whereas the hypercalcemia of hyperparathyroidism is generally resistant to this action of cortical hormone.

Patients with breast cancer tend to have lower excretion of gonadstimulating hormone in the urine than would be expected for their age and endocrine status. The significance or cause of this is not known, though it is shared by other chronic illnesses.

SUMMARY

Breast cancer is unusual in that its first signs of metastasis may appear many years after apparently successful surgical removal of the primary tumor. Breast cancer grows spasmodically rather than with smooth, even cadence. It metastasizes anywhere in the body, thus producing protean symptoms due to the space-occupying effects of the metastatic deposits. On occasion it produces proteinaceous substances which change the plasma levels of corticoid and thyroxine. In some way it inhibits the pituitary secretion of gonadotropin; it produces a sterol which affects the level of calcium and phosphorus in body fluids and probably accelerates induction of osteoporosis in the host.

As in all other malignant disease, there is a general decline in well-being and body activity due to the presence of the malignant disease. The tumor produces some toxic materials which we have not yet identified, since we frequently see patients who have died of metastatic disease with a rather small amount of malignant deposit, none of it in an area which would appear to be life-threatening, and with no evidence of the humoral production of physiologically active substances.

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